PRESCRIBING INFORMATION

ARRANON®

(nelarabine)

Injection

FOR INTRAVENOUS USE

WARNING

ARRANON® (nelarabine) Injection should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. This product is for intravenous use only.

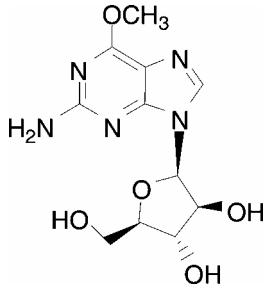
Neurologic Events: Severe neurologic events have been reported with the use of ARRANON. These events have included altered mental states including severe somnolence, central nervous system effects including convulsions, and peripheral neuropathy ranging from numbness and paresthesias to motor weakness and paralysis. There have also been reports of events associated with demyelination, and ascending peripheral neuropathies similar in appearance to Guillain-Barré syndrome.

Full recovery from these events has not always occurred with cessation of therapy with ARRANON. Close monitoring for neurologic events is strongly recommended, and ARRANON should be discontinued for neurologic events of NCI Common Toxicity Criteria grade 2 or greater.

DESCRIPTION

ARRANON (nelarabine) is a pro-drug of the cytotoxic deoxyguanosine analogue, 9-β-*D*-arabinofuranosylguanine (ara-G).

The chemical name for nelarabine is 2-amino-9-β-*D*-arabinofuranosyl-6-methoxy-9*H*-purine. It has the molecular formula $C_{11}H_{15}N_5O_5$ and a molecular weight of 297.27. Nelarabine has the following structural formula:



Nelarabine is slightly soluble to soluble in water and melts with decomposition between 209° and 217° C.

ARRANON Injection is supplied as a clear, colorless, sterile solution in glass vials. Each vial contains 250 mg of nelarabine (5 mg nelarabine per mL) and the inactive ingredient sodium chloride (4.5 mg per mL) in 50 mL Water for Injection, USP. ARRANON is intended for intravenous infusion.

Hydrochloric acid and sodium hydroxide may have been used to adjust the pH. The solution pH ranges from 5.0 to 7.0.

CLINICAL PHARMACOLOGY

Mechanism of Action: Nelarabine is a pro-drug of the deoxyguanosine analogue 9-β-*D*-arabinofuranosylguanine (ara-G). Nelarabine is demethylated by adenosine deaminase (ADA) to ara-G, mono-phosphorylated by deoxyguanosine kinase and deoxycytidine kinase, and subsequently converted to the active 5'-triphosphate, ara-GTP. Accumulation of ara-GTP in leukemic blasts allows for incorporation into deoxyribonucleic acid (DNA), leading to inhibition of DNA synthesis and cell death. Other mechanisms may contribute to the cytotoxic and systemic toxicity of nelarabine.

Pharmacokinetics: Pharmacokinetic studies in adult patients with refractory leukemia or lymphoma have demonstrated that nelarabine and ara-G are rapidly eliminated from plasma with a half-life of approximately 30 minutes and 3 hours, respectively after a 1,500 mg/m^2 nelarabine dose. No pharmacokinetic data are available in pediatric patients at the once daily 650 mg/m^2 nelarabine dose. Plasma ara-G C_{max} values generally occurred at the end of the nelarabine infusion and were generally higher than nelarabine C_{max} values, suggesting rapid and extensive conversion of nelarabine to ara-G. Mean plasma nelarabine and ara-G C_{max} values were 5.0 ± 3.0 μg/mL and 31.4 ± 5.6 μg/mL, respectively, after a 1,500 mg/m^2 nelarabine dose infused over 2 hours in adult patients. Exposure to ara-G (AUC) is 37 times higher than that for nelarabine on Day 1 after nelarabine IV infusion of 1,500 mg/m^2 dose (162 ± 49 μg.h/ml versus 4.4 ± 2.2 μg.h/ml, respectively). Comparable C_{max} and AUC were obtained for nelarabine between Days 1 and 5 at the proposed nelarabine adult dosage of 1,500 mg/m^2, indicating that the pharmacokinetics of nelarabine after multiple-dosing are predictable from single dosing. There are not enough data for ara-G to make a comparison between Day 1 and Day 5. After a nelarabine adult dosage of 1,500 mg/m^2, a mean intracellular C_{max} for ara-GTP appeared within 3 to 25 hours on Day 1. Exposure (AUC) to intracellular ara-GTP was 532 times higher than that for nelarabine and 14 times higher than that for ara-G (2,339 ± 2,628 μg.h/mL versus 4.4 ± 2.2 μg.h/mL and 162 ± 49 μg.h/mL, respectively). Because the intracellular levels of ara-GTP were so prolonged, its elimination half-life could not be accurately estimated.

Combined Phase 1 pharmacokinetic data at nelarabine doses of 104 to 2,900 mg/m^2 indicate that the mean clearance (CL) of nelarabine is about 30% higher in pediatric patients than in adult patients (259 ± 409 L/h/m^2 versus 197 ± 189 L/h/m^2, respectively) (n = 66 adults, n = 22 pediatric patients) on Day 1. The apparent clearance of Ara-G (CL/F) is comparable between the two groups (10.5 ± 4.5 L/h/m^2 in adult patients and 11.3 ± 4.2 L/h/m^2 in pediatric patients) on Day 1.

Nelarabine and ara-G are extensively distributed throughout the body. Specifically, for nelarabine, V_{SS} values were 197 ± 216 L/m^2 and 213 ± 358 L/m^2 in adult and pediatric patients, respectively. For ara-G, V_{SS}/F values were 50 ± 24 L/m^2 and 33 ± 9.3 L/m^2 in adult and pediatric patients, respectively.

Nelarabine and ara-G are not substantially bound to human plasma proteins (<25%) in vitro, and binding is independent of nelarabine or ara-G concentrations up to 600 μM.

Metabolism: The principal route of metabolism for nelarabine is O-demethylation by adenosine deaminase to form ara-G, which undergoes hydrolysis to form guanine. In addition, some nelarabine is hydrolyzed to form methylguanine, which is O-demethylated to form guanine. Guanine is N-deaminated to form xanthine, which is further oxidized to yield uric acid. Ring opening of uric acid followed by further oxidation results in the formation of allantoin.

Excretion: Nelarabine and ara-G are partially eliminated by the kidneys. Mean urinary excretion of nelarabine and ara-G was 6.6 ± 4.7% and 27 ± 15% of the administered dose, respectively, in 28 adult patients over the 24 hours after nelarabine infusion on Day 1. Renal clearance averaged 24 ± 23 L/h for nelarabine and 6.2 ± 5.0 L/h for ara-G in 21 adult patients.

Special Populations: ***Gender:*** Gender has no effect on nelarabine or ara-G pharmacokinetics.

Race: Most patients enrolled in Phase 1 studies were Whites. In general, nelarabine mean clearance and volume of distribution values tend to be higher in Whites (n = 63) than in Blacks (by about 10%) (n = 15). The opposite is true for ara-G; mean apparent clearance and volume of distribution values tend to be lower in Whites than in Blacks (by about 15-20%). No differences in safety or effectiveness were observed between these groups.

Geriatrics: Age has no effect on the pharmacokinetics of nelarabine or ara-G. Decreased renal function, which is more common in the elderly, may reduce ara-G clearance (see PRECAUTIONS, Geriatric Use).

Pediatrics: No pharmacokinetic data are available in pediatric patients at the once daily 650 mg/m^2 nelarabine dosage. Combined Phase 1 pharmacokinetic data at nelarabine doses of 104 to 2,900 mg/m^2 indicate that the mean clearance (CL) of nelarabine is about 30% higher in pediatric patients than in adult patients (259 ± 409 L/h/m^2 versus 197 ± 189 L/h/m^2, respectively) (n = 66 adults, n = 22 pediatric patients) on Day 1. The apparent clearance of ara-G (CL/F) is comparable between the two groups (10.5 ± 4.5 L/h/m^2 in adult patients and 11.3 ± 4.2 L/h/m^2 in pediatric patients) on Day 1.

Nelarabine and ara-G are extensively distributed throughout the body. Specifically, for nelarabine, V_{SS} values were 197 ± 216 L/m^2 and 213 ± 358 L/m^2 in adult and pediatric patients, respectively. For ara-G, V_{SS}/F values were 50 ± 24 L/m^2 and 33 ± 9.3 L/m^2 in adult and pediatric patients, respectively.

Renal Impairment: The pharmacokinetics of nelarabine and ara-G have not been specifically studied in renally impaired or hemodialyzed patients. Nelarabine is excreted by the kidney to a small extent (5 to 10% of the administered dose). Ara-G is excreted by the kidney to a greater extent (20 to 30% of the administered nelarabine dose). Patients were categorized into 3 groups: normal with CL_{cr} >80 mL/min (n = 67), mild with CL_{cr} = 50-80 mL/min (n = 15), and moderate with CL_{cr} <50 mL/min (n = 3). The mean apparent clearance (CL/F) of ara-G was about 15% and 40% lower in patients with mild and moderate renal impairment, respectively, than in patients with normal renal function (see PRECAUTIONS and DOSAGE AND

ADMINISTRATION). No differences in safety or effectiveness were observed.

Hepatic Impairment: The influence of hepatic impairment on the pharmacokinetics of nelarabine has not been evaluated.

Drug Interactions: Nelarabine and ara-G did not significantly inhibit the activities of the human hepatic cytochrome P450 isoenzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4 in vitro at concentrations of nelarabine and ara-G up to 100 μM.

Administration of fludarabine 30 mg/m^2 as a 30-minute infusion 4 hours before a 1,200 mg/m^2 infusion of nelarabine did not affect the pharmacokinetics of nelarabine, ara-G, or ara-GTP in 12 patients with refractory leukemia.

CLINICAL STUDIES

The safety and efficacy of ARRANON were evaluated in two open-label, single-arm, multicenter studies.

Pediatric Clinical Study: The safety and efficacy of ARRANON in pediatric patients were studied in a clinical trial conducted by the Children's Oncology Group (COG P9673). This study included patients 21 years of age and younger, who had relapsed or refractory T-cell acute lymphoblastic leukemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LBL). Eighty-four (84) patients, 39 of whom had received two or more prior induction regimens, were treated with 650 mg/m^2/day of ARRANON administered intravenously over 1 hour daily for 5 consecutive days repeated every 21 days (see Table 1). Patients who experienced signs or symptoms of grade 2 or greater neurologic toxicity on therapy were to be discontinued from further therapy with ARRANON.

Table 1. Pediatric Clinical Study - Patient Allocation

Patient Population	**N**
Patients treated at 650 mg/m^2/day x 5 days every 21 days.	84
Patients with T-ALL or T-LBL with two or more prior induction treated at 650 mg/m^2/day x 5 days every 21 days.	39
Patients with T-ALL or T-LBL with one prior induction treated at 650 mg/m^2/day x 5 days every 21 days.	31

The 84 patients ranged in age from 2.5-21.7 years (overall mean, 11.9 years), 52% were 3 to 12 years of age and most were male (74%) and Caucasian (62%). The majority (77%) of patients had a diagnosis of T-ALL.

Complete response (CR) in this study was defined as bone marrow blast counts ≤5%, no other evidence of disease, and full recovery of peripheral blood counts. Complete response without full hematologic recovery (CR*) was also assessed as a meaningful outcome in this heavily pretreated population. Duration of response is reported from date of response to date of relapse, and may include subsequent stem cell transplant. Efficacy results are presented in Table 2.

Table 2. Efficacy Results in Patients 21 Years of Age and Younger at Diagnosis With ≥2 Prior Inductions Treated with 650 mg/m^2 of ARRANON Administered Intravenously Over 1 Hour Daily for 5 Consecutive Days Repeated Every 21 Days

	N = 39
CR plus CR* % (n) [95% CI]	23% (9) [11%, 39%]
CR % (n) [95% CI]	13% (5) [4%, 27%]
CR* % (n) [95% CI]	10% (4) [3%, 24%]
Duration of CR plus CR* (range in weeks)[1]	3.3 to 9.3
Median overall survival (weeks) [95% CI]	13.1 [8.7, 17.4]

CR = Complete response

CR* = Complete response without hematologic recovery

[1] Does not include 5 patients who were transplanted or had subsequent systemic chemotherapy (duration of response in these 5 patients was 4.7 to 42.1 weeks).

The mean number of days on therapy was 46 days (range of 7 to 129 days). Median time to CR plus CR* was 3.4 weeks (95% CI: 3.0, 3.7).

Adult Clinical Study: The safety and efficacy of ARRANON in adult patients were studied in a clinical trial conducted by the Cancer and Leukemia Group B (CALGB). This study included 39 treated patients, 28 who had T-cell acute lymphoblastic leukemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LBL) that had relapsed following or was refractory to at least two prior induction regimens. ARRANON 1,500 mg/m^2 was administered intravenously over 2 hours on days 1, 3 and 5 repeated every 21 days. Patients who experienced signs or symptoms of grade 2 or greater neurologic toxicity on therapy were to be discontinued from further therapy with ARRANON. Seventeen patients had a diagnosis of T-ALL and 11 had a diagnosis of T-LBL. For patients with ≥2 prior inductions, the age range was 16-65 years (mean 34 years) and most patients were male (82%) and Caucasian (61%). Patients with central nervous system (CNS) disease were not eligible.

Complete response (CR) in this study was defined as bone marrow blast counts ≤5%, no other evidence of disease, and full recovery of peripheral blood counts. Complete response without complete hematologic recovery (CR*) was also assessed. The results of the study for patients who had received ≥2 prior inductions are shown in Table 3.

Table 3. Efficacy Results in Adult Patients With ≥2 Prior Inductions Treated with 1,500 mg/m^2 of ARRANON Administered Intravenously Over 2 Hours on Days 1, 3, and 5 Repeated Every 21 Days

	N = 28
CR plus CR* % (n) [95%CI]	21% (6) [8%, 41%]
CR % (n) [95%CI]	18% (5) [6%, 37%]
CR* % (n) [95%CI]	4% (1) [0%, 18%]
Duration of CR plus CR* (range in weeks)[1]	4 to 195+
Median overall survival (weeks) [95% CI]	20.6 weeks [10.4, 36.4]

CR = Complete response

CR* = Complete response without hematologic recovery

[1] Does not include 1 patient who was transplanted (duration of response was 156+ weeks).

The mean number of days on therapy was 56 days (range of 10 to 136 days). Time to CR plus CR* ranged from 2.9 to 11.7 weeks.

INDICATIONS AND USAGE

ARRANON is indicated for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens. This use is based on the induction of complete responses. Randomized trials demonstrating increased survival or other clinical benefit have not been conducted.

CONTRAINDICATIONS

ARRANON is contraindicated in patients who have a history of hypersensitivity to nelarabine or any other components of ARRANON.

WARNINGS

ARRANON should be administered under the supervision of a physician experienced in the use of antineoplastic therapy.

Neurologic Events (see boxed WARNING): ARRANON is a potent antineoplastic agent with potentially significant toxic side effects. Neurotoxicity is the dose-limiting toxicity of nelarabine. Patients undergoing therapy with ARRANON should be closely observed for signs and symptoms of neurologic toxicity.

Common signs and symptoms of nelarabine-related neurotoxicity include somnolence, confusion, convulsions, ataxia, paraesthesias, and hypoesthesia. Severe neurologic toxicity can manifest as coma, status epilepticus, craniospinal demyelination, or ascending neuropathy similar in presentation to Guillain-Barré syndrome.

Patients treated previously or concurrently with intrathecal chemotherapy or previously with craniospinal irradiation may be at increased risk for neurologic adverse events. See DOSAGE AND ADMINISTRATION.

Pregnancy Category D: ARRANON may cause fetal harm when administered to a pregnant woman. There are no studies of ARRANON in pregnant women. When compared to controls, nelarabine administration during the period of organogenesis caused increased incidences of fetal malformations, anomalies, and variations in rabbits at doses ≥360 mg/m^2/day (8-hour IV infusion; approximately ¼ the adult dose compared on a mg/m^2 basis), which was the lowest dose tested. Cleft palate was seen in rabbits given 3,600 mg/m^2/day (approximately 2-fold the adult dose), absent pollices (digits) in rabbits given ≥1,200 mg/m^2/day (approximately ¾ the adult dose), while absent gall bladder, absent accessory lung lobes, fused or extra sternebrae and delayed ossification was seen at all doses. Maternal body weight gain and fetal body weights were reduced in rabbits given 3,600 mg/m^2/day (approximately 2-fold the adult dose), but could not account for the increased incidence of malformations seen at this or lower administered doses. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be warned of the potential hazard to the fetus. Women of child-bearing potential should be advised to avoid becoming pregnant while receiving treatment with ARRANON.

PRECAUTIONS

Hematologic: Leukopenia, thrombocytopenia, anemia, and neutropenia, including febrile neutropenia have been associated with nelarabine therapy. Complete blood counts including platelets should be monitored regularly (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

General: Patients receiving ARRANON should receive intravenous hydration according to standard medical practice for the management of hyperuricemia in patients at risk for tumor lysis syndrome. Consideration should be given to the use of allopurinol in patients at risk of hyperuricemia.

Administration of live vaccines to immunocompromised patients should be avoided.

Information for Patients: Since patients receiving nelarabine therapy may experience somnolence, they should be cautioned about operating hazardous machinery, including automobiles.

Patients should be instructed to contact their physician if they experience new or worsening symptoms of peripheral neuropathy (see WARNINGS and DOSAGE and ADMINISTRATION). These signs and symptoms include: tingling or numbness in fingers, hands, toes, or feet; difficulty with the fine motor coordination tasks such as buttoning clothing; unsteadiness while walking; weakness arising from a low chair; weakness in climbing stairs; increased tripping while walking over uneven surfaces.

Patients should be instructed that seizures have been known to occur in patients who receive nelarabine. If a seizure occurs, the physician administering ARRANON should be promptly informed.

Patients who develop fever or signs of infection while on therapy should notify their physician promptly.

Patients should be advised to use effective contraceptive measures to prevent pregnancy and to avoid breast feeding during treatment with ARRANON.

Drug Interactions: Nelarabine and ara-G did not significantly inhibit the activities of the human hepatic cytochrome P450 isoenzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4 in vitro at concentrations of nelarabine and ara-G up to 100 μM.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity testing of nelarabine has not been done. However, nelarabine was mutagenic when tested in vitro in L5178Y/TK mouse lymphoma cells with and without metabolic activation. No studies have been conducted in animals to assess genotoxic potential or effects on fertility. The effect on human fertility is unknown.

Pregnancy: Pregnancy Category D. (See WARNINGS.)

Nursing Mothers: It is not known whether nelarabine or ara-G are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ARRANON, nursing should be discontinued in women who are receiving therapy with ARRANON.

Pediatric Use: (See CLINICAL STUDIES, Pediatric Clinical Study).

Geriatric Use: Clinical studies of ARRANON did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In an exploratory analysis, increasing age, especially age 65 years and older, appeared to be associated with increased rates of neurologic adverse events.

Use in Renally Impaired Patients: Ara-G clearance decreased as renal function decreased (see CLINICAL PHARMACOLOGY). Because the risk of adverse reactions to this drug may be greater in patients with severe renal impairment (CL_{cr} <30 mL/min), these patients should be closely monitored for toxicities when treated with ARRANON (see DOSAGE AND ADMINISTRATION).

Use in Hepatically Impaired Patients: The influence of hepatic impairment on the pharmacokinetics of nelarabine has not been evaluated. Because the risk of adverse reactions to this drug may be greater in patients with severe hepatic impairment (bilirubin >3.0 mg/dL), these patients should be closely monitored for toxicities when treated with ARRANON.

ADVERSE REACTIONS

ARRANON was studied in 459 patients in Phase I and Phase II clinical trials. The safety profile for the recommended dosages of ARRANON is based on data from 103 adult patients enrolled and treated in the CALGB 19801 and an adult chronic lymphocytic leukemia study (PGAA2003) who were treated with the recommended dose and schedule. The safety profile for children is based on data from 84 pediatric patients enrolled and treated in the COG P9673 study who were treated with the recommended dose and schedule.

The most common adverse events in pediatric patients, regardless of causality, were hematologic disorders (anemia, leukopenia, neutropenia, and thrombocytopenia). Of the non-hematologic adverse events in pediatric patients, the most frequent events reported were

headache, increased transaminase levels, decreased blood potassium, decreased blood albumin, increased blood bilirubin, and vomiting.

The most common adverse events in adults, regardless of causality, were fatigue; gastrointestinal (GI) disorders (nausea, diarrhea, vomiting, and constipation); hematologic disorders (anemia, neutropenia, and thrombocytopenia); respiratory disorders (cough and dyspnea); nervous system disorders (somnolence and dizziness); and pyrexia.

The most common adverse events by System Organ Class, regardless of causality, including severe or life threatening events (NCI Common Toxicity Criteria grade 3 or grade 4) and fatal events (grade 5) are shown in Table 4 for pediatric patients and Table 5 for adult patients.

Table 4. Most Commonly Reported (≥5% Overall) Adverse Events Regardless of Causality in Pediatric Patients Treated with 650 mg/m^2 of ARRANON Administered Intravenously Over 1 Hour Daily for 5 Consecutive Days Repeated Every 21 Days

	Percentage of Patients: 650 mg/m^2; N = 84		
	Toxicity Grade		
System Organ Class Preferred Term	**Grade 3 %**	**Grade 4+ %**	**All Grades %**
Blood and Lymphatic System Disorders			
Anemia	45	10	95
Neutropenia	17	62	94
Thrombocytopenia	27	32	88
Leukopenia	14	7	38
Hepatobiliary Disorders			
Transaminases increased	4	0	12
Blood albumin decreased	5	1	10
Blood bilirubin increased	7	2	10
Metabolic/Laboratory			
Blood potassium decreased	4	2	11
Blood calcium decreased	1	1	8
Blood creatinine increased	0	0	6
Blood glucose decreased	4	0	6
Blood magnesium decreased	2	0	6
Nervous System Disorders (see Table 6)			
Gastrointestinal Disorders			
Vomiting	0	0	10
General Disorders & Administration Site Conditions			
Asthenia	1	0	6
Infections & Infestations			
Infection	2	1	5

Grade 4+ = Grade 4 and Grade 5

Three (3) patients had a fatal event. Fatal events included neutropenia and pyrexia (n = 1), status epilepticus/seizure (n = 1), and fungal pneumonia (n = 1). The status epilepticus was thought to be related to treatment with ARRANON. All other fatal events were unrelated to treatment with ARRANON.

Table 5: Most Commonly Reported (≥5% Overall) Adverse Events Regardless of Causality in Adult Patients Treated with 1,500 mg/m^2 of ARRANON Administered Intravenously Over 2 Hours on Days 1, 3, and 5 Repeated Every 21 Days

	Percentage of Patients; N = 103		
	Toxicity Grade		
System Organ Class Preferred Term	**Grade 3 %**	**Grade 4+ %**	**All Grades %**
Blood and Lymphatic System Disorders			
Anemia	20	14	99
Thrombocytopenia	37	22	86
Neutropenia	14	49	81
Febrile neutropenia	9	1	12
Cardiac Disorders			
Sinus tachycardia	1	0	8
Gastrointestinal Disorders			
Nausea	0	0	41
Diarrhea	1	0	22
Vomiting	1	0	22
Constipation	1	0	21
Abdominal pain	1	0	9
Stomatitis	1	0	8
Abdominal distension	0	0	6
General Disorders and Administration Site Conditions			
Fatigue	10	2	50
Pyrexia	5	0	23
Asthenia	0	1	17
Edema, peripheral	0	0	15
Edema	0	0	11
Pain	3	0	11
Rigors	0	0	8
Gait, abnormal	0	0	6
Chest pain	0	0	5
Non-cardiac chest pain	0	1	5
Infections			
Infection	2	1	9
Pneumonia	4	1	8
Sinusitis	1	0	7
Hepatobiliary Disorders			
AST increased	1	1	6
Metabolism and Nutrition Disorders			
Anorexia	0	0	9
Dehydration	3	1	7
Hyperglycemia	1	0	6
Musculoskeletal and Connective Tissue Disorders			
Myalgia	1	0	13
Arthralgia	1	0	9
Back pain	0	0	8

System Organ Class Preferred Term	Percentage of Patients; N = 103 Toxicity Grade Grade 3 %	Grade 4+ %	All Grades %
Muscular weakness	5	0	8
Pain in extremity	1	0	7
Nervous System Disorders (see Table 7)			
Psychiatric Disorders			
Confusional state	2	0	8
Insomnia	0	0	7
Depression	1	0	6
Respiratory, Thoracic, and Mediastinal Disorders			
Cough	0	0	25
Dyspnea	4	2	20
Pleural effusion	5	1	10
Epistaxis	0	0	8
Dyspnea, exertional	0	0	7
Wheezing	0	0	5
Vascular Disorders			
Petechiae	2	0	12
Hypotension	1	1	8

Grade 4+ = Grade 4 and Grade 5

Five (5) patients had a fatal event. Fatal events included hypotension (n = 1), respiratory arrest (n = 1), pleural effusion/pneumothorax (n = 1), pneumonia (n = 1), and cerebral hemorrhage/coma/leukoencephalopathy (n = 1). The cerebral hemorrhage/coma/leukoencephalopathy was thought to be related to treatment with ARRANON. All other fatal events were unrelated to treatment with ARRANON.

Other Adverse Events: Blurred vision was also reported in 4% of adult patients.

There was a single report of biopsy confirmed progressive multifocal leukoencephalopathy in the adult patient population.

Neurologic Adverse Events: Nervous system events, regardless of drug relationship, were reported for 64% of patients across the Phase I and Phase II studies.

Pediatric: The most common neurologic adverse events (≥2%), regardless of causality, including all grades (NCI Common Toxicity Criteria) are shown in Table 6 for pediatric patients.

Table 6: Neurologic Adverse Events (≥2%) Regardless of Causality in Pediatric Patients Treated with 650 mg/m^2 of ARRANON Administered Intravenously Over 1 Hour Daily for 5 Consecutive Days Repeated Every 21 Days

	Percentage of Patients; N = 84				
Nervous System Disorders Preferred Term	**Grade 1 %**	**Grade 2 %**	**Grade 3 %**	**Grade 4+ %**	**All Grades %**
Headache	8	2	4	2	17
Peripheral neurologic disorders, any event	1	4	7	0	12
Peripheral neuropathy	0	4	2	0	6
Peripheral motor neuropathy	1	0	2	0	4
Peripheral sensory neuropathy	0	0	6	0	6
Somnolence	1	4	1	1	7
Hypoesthesia	1	1	4	0	6
Seizures	0	0	0	6	6
Convulsions	0	0	0	3	4
Grand mal convulsions	0	0	0	1	1
Status epilepticus	0	0	0	1	1
Motor dysfunction	1	1	1	0	4
Nervous system disorder	1	2	0	0	4
Paresthesia	0	2	1	0	4
Tremor	1	2	0	0	4
Ataxia	1	0	1	0	2

Grade 4+ = Grade 4 and Grade 5

One (1) patient had a fatal neurologic event, status epilepticus. This event was thought to be related to treatment with ARRANON.

The other grade 3 event in pediatric patients, regardless of causality, was hypertonia reported in 1 patient (1%). The additional grade 4+ events, regardless of causality, were 3rd nerve paralysis, and 6th nerve paralysis, each reported in 1 patient (1%).

The other neurologic adverse events, regardless of causality, reported as grade 1, 2, or unknown in pediatric patients were dysarthria, encephalopathy, hydrocephalus, hyporeflexia, lethargy, mental impairment, paralysis, and sensory loss, each reported in 1 patient (1%).

Adults: The most common neurologic adverse events (≥2%), regardless of causality, including all grades (NCI Common Toxicity Criteria) are shown in Table 7 for adult patients.

Table 7: Neurologic Adverse Events (≥2%) Regardless of Causality in Adult Patients Treated with 1,500 mg/m^2 of ARRANON Administered Intravenously Over 2 Hours on Days 1, 3, and 5 Repeated Every 21 Days

	Percentage of Patients; N =103				
System Organ Class Preferred Term	**Grade 1 %**	**Grade 2 %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**
Somnolence	20	3	0	0	23
Dizziness	14	8	0	0	21
Peripheral neurologic disorders, any event	8	12	2	0	21
Neuropathy	0	4	0	0	4
Peripheral neuropathy	2	2	1	0	5
Peripheral motor neuropathy	3	3	1	0	7
Peripheral sensory neuropathy	7	6	0	0	13
Hypoesthesia	5	10	2	0	17
Headache	11	3	1	0	15
Paresthesia	11	4	0	0	15
Ataxia	1	6	2	0	9
Depressed level of consciousness	4	1	0	1	6
Tremor	2	3	0	0	5
Amnesia	2	1	0	0	3
Dysgeusia	2	1	0	0	3
Balance disorder	1	1	0	0	2
Sensory loss	0	2	0	0	2

One (1) patient had a fatal neurologic event, cerebral hemorrhage/coma/leukoencephalopathy. This event was thought to be related to treatment with ARRANON.

Most nervous system events in the adult patients were evaluated as grade 1 or 2. The additional grade 3 events in adult patients, regardless of causality, were aphasia, convulsion, hemiparesis, and loss of consciousness, each reported in 1 patient (1%). The additional grade 4 events, regardless of causality, were cerebral hemorrhage, coma, intracranial hemorrhage, leukoencephalopathy, and metabolic encephalopathy, each reported in one patient (1%).

The other neurologic adverse events, regardless of causality, reported as grade 1, 2, or unknown in adult patients were abnormal coordination, burning sensation, disturbance in attention, dysarthria, hyporeflexia, neuropathic pain, nystagmus, peroneal nerve palsy, sciatica, sensory disturbance, sinus headache, and speech disorder, each reported in one patient (1%).

Other Neurologic Events: There have also been reports of events associated with demyelination and ascending peripheral neuropathies similar in appearance to Guillain-Barré syndrome.

OVERDOSAGE

There is no known antidote for overdoses of ARRANON. It is anticipated that overdosage would result in severe neurotoxicity (possibly including paralysis, coma), myelosuppression, and

potentially death. In the event of overdose, supportive care consistent with good clinical practice should be provided.

Nelarabine has been administered in clinical trials up to a dose of 2,900 mg/m^2 on days 1, 3, and 5 to 2 adult patients. At a dose of 2,200 mg/m^2 given on days 1, 3, and 5 every 21 days, 2 patients developed a significant grade 3 ascending sensory neuropathy. MRI evaluations of the 2 patients demonstrated findings consistent with a demyelinating process in the cervical spine.

A single IV dose of 4,800 mg/m^2 was lethal in monkeys, and was associated with CNS signs including reduced/shallow respiration, reduced reflexes, and flaccid muscle tone.

DOSAGE AND ADMINISTRATION

Preparation for Administration: ARRANON is not diluted prior to administration. The appropriate dose of ARRANON is transferred into polyvinylchloride (PVC) infusion bags or glass containers and administered as a two-hour infusion in adult patients and as a one-hour infusion in pediatric patients.

Prior to administration, inspect the drug product visually for particulate matter and discoloration.

Adult Dosage: The recommended adult dose of ARRANON is 1,500 mg/m² administered intravenously over 2 hours on days 1, 3, and 5 repeated every 21 days. ARRANON is administered undiluted.

Pediatric Dosage: The recommended pediatric dose of ARRANON is 650 mg/m² administered intravenously over 1 hour daily for 5 consecutive days repeated every 21 days. ARRANON is administered undiluted.

The recommended duration of treatment for adult and pediatric patients has not been clearly established. In clinical trials, treatment was generally continued until there was evidence of disease progression, the patient experienced unacceptable toxicity**,** the patient became a candidate for bone marrow transplant**,** or the patient no longer continued to benefit from treatment.

Supportive Care: Appropriate measures (e.g., hydration, urine alkalinization, and prophylaxis with allopurinol) must be taken to prevent hyperuricemia of tumor lysis syndrome.

Dose Modification: ARRANON should be discontinued for neurologic events of NCI Common Toxicity Criteria grade 2 or greater. Dosage may be delayed for other toxicity including hematologic toxicity.

Adjustment of Dose in Special Populations: ARRANON has not been studied in patients with hepatic or renal dysfunction (see PRECAUTIONS). No dose adjustment is recommended for patients with a CL_{cr} ≥50 mL/min (see CLINICAL PHARMACOLOGY, Renal Impairment). There are insufficient data to support a dose recommendation for CL_{cr} <50 mL/min.

Precautions: ARRANON is a cytotoxic agent. Caution should be used during handling and preparation. Use of gloves and other protective clothing to prevent skin contact is recommended. Proper aseptic technique should be used.

Stability: Nelarabine Injection is stable in polyvinylchloride (PVC) infusion bags and glass containers for up to 8 hours at up to 30° C.

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be used. Several guidelines on this subject have been published.[1-9]

There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

ARRANON Injection is supplied as a clear, colorless, sterile solution in Type I, clear glass vials with a gray butyl rubber (latex-free) stopper and a red snap-off aluminum seal. Each vial contains 250 mg of nelarabine (5 mg nelarabine per mL) and the inactive ingredient sodium chloride (4.5 mg per mL) in 50 mL Water for Injection, USP. Vials are available in the following carton sizes:

NDC 0007-4401-01 (package of 1)

NDC 0007-4401-06 (package of 6)

Store at 25° C (77° F); excursions permitted to 15° to 30° C (59° to 86° F) [see USP Controlled Room Temperature].

REFERENCES

1. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice. Pittsburgh, PA: Oncology Nursing Society; 1999:32-41.
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3. AMA Council on Scientific Affairs. Guidelines for handling parenteral antineoplastics. *JAMA.* 1985;253:1590-1591.
4. National Study Commission on Cytotoxic Exposure. Recommendations for handling cytotoxic agents. 1987. Available from Louis P. Jeffrey, Chairman, National Study Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.
5. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Australia.* 1983;1:426-428.
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7. American Society of Hospital Pharmacists. ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm.* 1990;47:1033-1049.
8. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines.) *Am J Health-Syst Pharm.* 1996;53:1669-1685.
9. Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. NIOSH Alert 2004-165.

GlaxoSmithKline
Research Triangle Park, NC 27709

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PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION LEAFLET
ARRANON® (AIR-ra-non)
Nelarabine Injection

Read the Patient Information that comes with ARRANON before you or your child start treatment with ARRANON. Read the information you get each time before each treatment with ARRANON. There may be new information. This information does not take the place of talking with the doctor about your or your child's medical condition or treatment. Talk to your or your child's doctor, if you have any questions.

What is the most important information I should know about ARRANON?

ARRANON may cause serious nervous system problems including:

- **extreme sleepiness**
- **seizures**
- **coma**
- **numbness and tingling in the hands, fingers, feet, or toes (peripheral neuropathy)**
- **weakness and paralysis**

Call the doctor right away if you or your child has the following symptoms:

- seizures
- numbness and tingling in the hands, fingers, feet, or toes
- problems with fine motor skills such as buttoning clothes
- unsteady while walking
- increased tripping while walking
- weakness when getting out of a chair or walking up stairs

These symptoms may not go away even when treatment with ARRANON is stopped.

What is ARRANON?

ARRANON is an anti-cancer medicine used to treat adults and children who have:

- T-cell acute lymphoblastic leukemia
- T-cell lymphoblastic lymphoma

Who should not take ARRANON?

You or your child should not take ARRANON if you or your child are allergic to nelarabine, or to anything else in ARRANON.

What should I tell the doctor before I or my child starts ARRANON?

Tell the doctor about all health conditions you or your child have, including if you or your child:

- **have any nervous system problems.**
- **have kidney problems.**
- **are pregnant or plan to become pregnant.** ARRANON may harm an unborn baby. You should use effective birth control to avoid getting pregnant. Talk with your doctor about your choices.
- **are breast feeding.** It is not known whether ARRANON passes through breast milk. You should not breast feed during treatment with ARRANON.

Tell the doctor about all the medicines you or your child take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

How is ARRANON given?

- ARRANON is an IV medicine. This means it is given through a tube in your vein.

What should I or my child avoid during treatment with ARRANON?

- **You or your child should not drive or operate dangerous machines.** ARRANON may cause sleepiness.
- **You or your child should not receive vaccines made with live germs during treatment with ARRANON.**

What are the possible side effects of ARRANON?

ARRANON may cause serious nervous system problems. See "What is the most important information I should know about ARRANON?"

ARRANON may also cause:

- **decreased blood counts** such as low red blood cells, low white blood cells, and low platelets. Call the doctor right away if you or your child:
    - is more tired than usual, pale, or has trouble breathing
    - has a fever or other signs of an infection
    - bruises easy or has any unusual bleeding

  Blood tests should be done regularly to check blood counts.
    - **stomach area problems** such as nausea, vomiting, diarrhea, and constipation
    - headache
    - sleepiness
    - blurry eyesight

These are not all the side effects with ARRANON. Ask your doctor or pharmacist for more information.

General Advice about ARRANON

This leaflet summarizes important information about ARRANON. If you have questions or problems, talk with your or your child's doctor. You can ask your doctor or pharmacist for information about ARRANON that is written for healthcare providers or it is available at www.GSK.com.

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