HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ARRANON safely and effectively. See full prescribing information for ARRANON.

ARRANON (nelarabine) Injection
Initial U.S. Approval: 2005

WARNING: NEUROLOGIC ADVERSE REACTIONS

See full prescribing information for complete boxed warning.

Severe neurologic adverse reactions have been reported with the use of ARRANON. These adverse reactions 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 adverse reactions associated with demyelination, and ascending peripheral neuropathies similar in appearance to Guillain-Barré syndrome. (5.1)

Full recovery from these adverse reactions has not always occurred with cessation of therapy with ARRANON. Close monitoring for neurologic adverse reactions is strongly recommended, and ARRANON should be discontinued for neurologic adverse reactions of NCI Common Toxicity Criteria grade 2 or greater. (5.1)

INDICATIONS AND USAGE

ARRANON is a nucleoside metabolic inhibitor 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. (1)

DOSAGE AND ADMINISTRATION

- Adult dose: 1,500 mg/m² administered intravenously over 2 hours on days 1, 3, and 5 repeated every 21 days. (2.1)
- Pediatric dose: 650 mg/m² administered intravenously over 1 hour daily for 5 consecutive days repeated every 21 days. (2.1)
- Discontinue treatment for ≥grade 2 neurologic reactions. (2.2)
- Dosage may be delayed for hematologic reactions (2.2)
- Take measures to prevent hyperuricemia. (2.4)

DOSAGE FORMS AND STRENGTHS

250 mg/50 mL (5 mg/mL) vial (3)

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

- Severe neurologic reactions have been reported. Monitor for signs and symptoms of neurologic toxicity. (5.1)
- Hematologic Reactions: Complete blood counts including platelets should be monitored regularly. (5.2)
- Fetal harm can occur if administered to a pregnant woman. Women should be advised not to become pregnant when taking ARRANON. (5.3)

ADVERSE REACTIONS

The most common (≥ 20%) adverse reactions were:

- Adult: anemia, thrombocytopenia, neutropenia, nausea, diarrhea, vomiting, constipation, fatigue, pyrexia, cough, and dyspnea (6.1)
- Pediatric: anemia, neutropenia, thrombocytopenia and leukopenia (6.1)

The most common (>10%) neurological adverse reactions were:

- Adult: somnolence, dizziness, peripheral neurologic disorders, hypoesthesia, headache, and paresthesia (6.1)
- Pediatric: headache and peripheral neurologic disorders (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Administration in combination with adenosine deaminase inhibitors, such as pentostatin, is not recommended. (7, 12.3)

USE IN SPECIFIC POPULATIONS

- Renal Impairment: Closely monitor patients with moderate or severe renal impairment for toxicities. (8.6)
- Hepatic Impairment: Closely monitor patients with severe hepatic impairment for toxicities. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: Month YEAR
ARR:XPI

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: NEUROLOGIC ADVERSE REACTIONS

Severe neurologic adverse reactions have been reported with the use of ARRANON. These adverse reactions 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 adverse reactions associated with demyelination, and ascending peripheral neuropathies similar in appearance to Guillain-Barré syndrome *[see Warnings and Precautions (5.1)]*.

Full recovery from these adverse reactions has not always occurred with cessation of therapy with ARRANON. Close monitoring for neurologic adverse reactions is strongly recommended, and ARRANON should be discontinued for neurologic adverse reactions of NCI Common Toxicity Criteria grade 2 or greater *[see Warnings and Precautions (5.1)]*.

1 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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

This product is for intravenous use only.

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.

Adult Dosage: The recommended adult dose of ARRANON is 1,500 mg/m^2 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/m^2 administered intravenously over 1 hour daily for 5 consecutive days repeated every 21 days. ARRANON is administered undiluted.

2.2 Dosage Modification

ARRANON administration should be discontinued for neurologic adverse reactions of NCI Common Toxicity Criteria grade 2 or greater. Dosage may be delayed for other toxicity including hematologic toxicity. *[See Boxed Warning and Warnings and Precautions (5.1, 5.2).]*

2.3 Adjustment of Dose in Special Populations

ARRANON has not been studied in patients with renal or hepatic dysfunction *[see Use in Specific Populations (8.6, 8.7)]*. No dose adjustment is recommended for patients with a creatinine clearance (CL_{cr}) ≥50 mL/min *[see Clinical Pharmacology (12.3)]*. There are insufficient data to support a dose recommendation for patients with a CL_{cr} <50 mL/min.

2.4 Prevention of Hyperuricemia

Appropriate measures (e.g., hydration, urine alkalinization, and prophylaxis with allopurinol) must be taken to prevent hyperuricemia *[see Warnings and Precautions (5.4)]*.

2.5 Instructions for Handling, Preparation, and Administration

Handling: 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. Guidelines for proper handling and disposal of anticancer drugs have been published.[1-4]

Preparation and Administration: Do not dilute ARRANON 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.

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

3 DOSAGE FORMS AND STRENGTHS

250 mg/50 mL (5 mg/mL) vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Neurologic Adverse Reactions

Neurotoxicity is the dose-limiting toxicity of nelarabine. Patients undergoing therapy with ARRANON should be closely observed for signs and symptoms of neurologic toxicity *[see Boxed Warning and Dosage and Administration (2.2)]*. Common signs and symptoms of nelarabine-related neurotoxicity include somnolence, confusion, convulsions, ataxia, paresthesias, 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.

5.2 Hematologic Adverse Reactions

Leukopenia, thrombocytopenia, anemia, and neutropenia, including febrile neutropenia have been associated with nelarabine therapy. Complete blood counts including platelets should be monitored regularly *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

5.3 Pregnancy

Pregnancy Category D

ARRANON can cause fetal harm when administered to a pregnant woman.

Nelarabine administered during the period of organogenesis caused increased incidences of fetal malformations, anomalies, and variations in rabbits *(see Use in Specific Populations (8.1)]*.

There are no adequate and well-controlled studies of ARRANON in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of child-bearing potential should be advised to avoid becoming pregnant while receiving treatment with ARRANON.

5.4 Hyperuricemia

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 *[see Dosage and Administration (2.4)]*.

5.5 Vaccinations

Administration of live vaccines to immunocompromised patients should be avoided.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Neurologic *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Hematologic *[see Warnings and Precautions (5.2)]*
- Hyperuricemia *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

ARRANON was studied in 459 patients in Phase I and Phase II clinical trials.

Adults: The safety profile of ARRANON is based on data from 103 adult patients treated with the recommended dose and schedule in 2 studies: an adult T-cell acute lymphoblastic leukemia (T-ALL)/T-cell lymphoblastic lymphoma (T-LBL) study and an adult chronic lymphocytic leukemia study.

The most common adverse reactions 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 reactions in adults, by System Organ Class, regardless of causality, including severe or life threatening adverse reactions (NCI Common Toxicity Criteria grade 3 or grade 4) and fatal adverse reactions (grade 5) are shown in Table 1.

Table 1. Most Commonly Reported (≥5% Overall) Adverse Reactions 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

System Organ Class Preferred Term	Percentage of Patients (N = 103)		
	Toxicity Grade		
	Grade 3 %	Grade 4 and 5[a] %	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

System Organ Class Preferred Term	Percentage of Patients (N = 103)		
	Toxicity Grade		
	Grade 3 %	Grade 4 and 5[a] %	All Grades %
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
Muscular weakness	5	0	8
Pain in extremity	1	0	7
Nervous System Disorders (see Table 2)			
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

[a] Five patients had a fatal adverse reaction. Fatal adverse reactions included hypotension (n = 1), respiratory arrest (n = 1), pleural effusion/pneumothorax (n = 1), pneumonia (n = 1), and cerebral hemorrhage/coma/leukoencephalopathy (n = 1).

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 Reactions: Nervous system adverse reactions, regardless of drug relationship, were reported for 76% of adult patients across the Phase I and Phase II studies. The most common neurologic adverse reactions (≥2%) in adult patients, regardless of causality, including all grades (NCI Common Toxicity Criteria) are shown in Table 2.

Table 2. Neurologic Adverse Reactions (≥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)				
Nervous System Disorders **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 adverse reaction	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 patient had a fatal neurologic adverse reaction, cerebral hemorrhage/coma/leukoencephalopathy.

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

The other neurologic adverse reactions, 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%).

Pediatrics: The safety profile for children is based on data from 84 pediatric patients treated with the recommended dose and schedule in a T-cell acute lymphoblastic leukemia (T-ALL)/T-cell lymphoblastic lymphoma (T-LBL) treatment study.

The most common adverse reactions in pediatric patients, regardless of causality, were hematologic disorders (anemia, leukopenia, neutropenia, and thrombocytopenia). Of the non-hematologic adverse reactions in pediatric patients, the most frequent adverse reactions reported were headache, increased transaminase levels, decreased blood potassium, decreased blood albumin, increased blood bilirubin, and vomiting.

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

Table 3. Most Commonly Reported (≥5% Overall) Adverse Reactions 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

System Organ Class Preferred Term	Percentage of Patients (N = 84) Toxicity Grade Grade 3 %	Grade 4 and 5[a] %	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 4)			
Gastrointestinal Disorders			
Vomiting	0	0	10
General Disorders & Administration Site Conditions			
Asthenia	1	0	6
Infections & Infestations			
Infection	2	1	5

[a] Three patients had a fatal adverse reaction. Fatal adverse reactions included neutropenia and pyrexia (n = 1), status epilepticus/seizure (n = 1), and fungal pneumonia (n = 1).

Neurologic Adverse Reactions: Nervous system adverse reactions, regardless of drug relationship, were reported for 42% of pediatric patients across the Phase I and Phase II studies. The most common neurologic adverse reactions (≥2%) in pediatric patients, regardless of causality, including all grades (NCI Common Toxicity Criteria) are shown in Table 4.

Table 4. Neurologic Adverse Reactions (≥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

Nervous System Disorders Preferred Term	Percentage of Patients (N = 84)				
	Grade 1 %	Grade 2 %	Grade 3 %	Grade 4 and 5[a] %	All Grades %
Headache	8	2	4	2	17
Peripheral neurologic disorders, any adverse reaction	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

[a] One (1) patient had a fatal neurologic adverse reaction, status epilepticus.

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

The other neurologic adverse reactions, 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%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ARRANON. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and Infestations: Fatal opportunistic infections.

Metabolism and Nutrition Disorders: Tumor lysis syndrome.

Nervous System Disorders: Demyelination and ascending peripheral neuropathies similar in appearance to Guillain-Barré syndrome.

7 DRUG INTERACTIONS

Administration of nelarabine in combination with adenosine deaminase inhibitors, such as pentostatin, is not recommended *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.3)]*

ARRANON can cause fetal harm when administered to a pregnant woman. Nelarabine administered to rabbits during the period of organogenesis caused increased incidences of fetal malformations, anomalies, and variations 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.

There are no adequate and well-controlled studies of ARRANON in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of child-bearing potential should be advised to avoid becoming pregnant while receiving treatment with ARRANON.

8.3 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, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of ARRANON has been established in pediatric patients *[see Dosage and Administration (2.1) and Clinical Studies (14.2]*.

8.5 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 reactions. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Renal Impairment

Ara-G clearance decreased as renal function decreased *[see Clinical Pharmacology (12.3)]*. Because the risk of adverse reactions to this drug may be greater in patients with moderate (CL_{cr} 30 to 50 mL/min) or severe (CL_{cr} <30 mL/min) renal impairment, these patients should be closely monitored for toxicities when treated with ARRANON *[see Dosage and Administration (2.3)]*.

8.7 Hepatic Impairment

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 (total bilirubin>3 times upper limit of normal), these patients should be closely monitored for toxicities when treated with ARRANON.

10 OVERDOSAGE

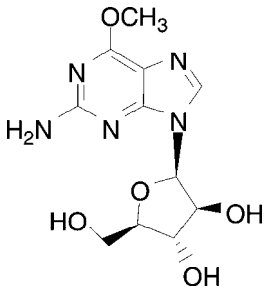
There is no known antidote for overdoses of ARRANON. It is anticipated that overdosage would result in severe neurotoxicity (possibly including paralysis, coma), myelosuppression, and potentially death. In the event of overdose, supportive care consistent with good clinical practice should be provided.

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.

11 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nelarabine is a pro-drug of the deoxyguanosine analogue 9-β-*D*-arabinofuranosylguanine (ara-G), a nucleoside metabolic inhibitor. 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.

12.3 Pharmacokinetics

Absorption: Following intravenous administration of nelarabine to adult patients with refractory leukemia or lymphoma, 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. The area under the concentration-time curve (AUC) of ara-G 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 values were obtained for nelarabine between Days 1 and 5 at the nelarabine adult dosage of 1,500 mg/m^2, indicating that nelarabine does not accumulate after multiple-dosing. There are not enough ara-G data to make a comparison between Day 1 and Day 5. After a nelarabine adult dose of 1,500 mg/m^2, 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.

Distribution: Nelarabine and ara-G are extensively distributed throughout the body. For nelarabine, V_{SS} values were 197 ± 216 L/m^2 in adult patients. For ara-G, V_{SS}/F values were 50 ± 24 L/m^2 in adult patients.

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.

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. Combined Phase 1 pharmacokinetic data at nelarabine doses of 199 to 2,900 mg/m^2 (n = 66 adult patients) indicate that the mean clearance (CL) of nelarabine is 197 ± 189 L/h/m^2 on Day 1. The apparent clearance of ara-G (CL/F) is 10.5 ± 4.5 L/h/m^2 on Day 1. Nelarabine and ara-G are rapidly eliminated from plasma with a mean half-life of 18 minutes and 3.2 hours, respectively, in adult patients.

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. For nelarabine, V_{SS} values were 213 ± 358 L/m^2 in pediatric patients. For ara-G, V_{SS}/F values were 33 ± 9.3 L/m^2 in pediatric patients. Nelarabine and ara-G are rapidly eliminated from plasma in pediatric patients, with a half-life of 13 minutes and 2 hours, respectively.

Effect of Age: Age has no effect on the pharmacokinetics of nelarabine or ara-G in adults. Decreased renal function, which is more common in the elderly, may reduce ara-G clearance *[see Use in Specific Populations (8.5)*.

Effect of Gender: Gender has no effect on nelarabine or ara-G pharmacokinetics.

Effect of Race: 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.

Effect of 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). In the combined Phase 1 studies, 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 Use in Specific Populations (8.6) and Dosage and Administration (2.3)]*. No differences in safety or effectiveness were observed.

Effect of Hepatic Impairment: The influence of hepatic impairment on the pharmacokinetics of nelarabine has not been evaluated *[see Use in Specific Populations (8.7)]*.

Drug Interactions: *Cytochrome P450:* 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.

Fludarabine: 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.

Pentostatin: There is in vitro evidence that pentostatin is a strong inhibitor of adenosine deaminase. Inhibition of adenosine deaminase may result in a reduction in the conversion of the pro-drug nelarabine to its active moiety and consequently in a reduction in efficacy of nelarabine and/or change in adverse reaction profile of either drug *[see Drug Interactions (7)*.

13 NONCLINICAL TOXICOLOGY

13.1 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.

14 CLINICAL STUDIES

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

14.1 Adult Clinical Study

The safety and efficacy of ARRANON in adult patients were studied in a clinical trial which 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. A 1,500 mg/m^2 dose of ARRANON 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 5.

Table 5. 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)[a]	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

[a] 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.

14.2 Pediatric Clinical Study

The safety and efficacy of ARRANON in pediatric patients were studied in a clinical trial which 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 6). 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 6. 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 7.

Table 7. 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)[a]	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
[a] 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).

15 REFERENCES

1. Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. NIOSH Alert 2004-165.
2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
3. American Society of Health-System Pharmacists. ASHP Guidelines on Handling Hazardous Drugs. *Am J Health-Syst Pharm*. 2006;63:1172-1193.
4. Polovich M, White JM, Kelleher LO (eds.) 2005. Chemotherapy and Biotherapy Guidelines and Recommendations for Practice. (2nd ed) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

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 0007-4401-06 (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].

17 PATIENT COUNSELING INFORMATION

Patient labeling is provided as a tear-off leaflet at the end of this full prescribing information. However, inform the patients of the following:

- 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 Boxed Warning, Warnings and Precautions (5.1), and Dosage and Administration (2.3)]*. 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.

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GlaxoSmithKline
Research Triangle Park, NC 27709

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
- unsteadiness 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

What should you tell the doctor before you or your 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 breast-feeding or plan to breast-feed. It is not known whether ARRANON passes through breast milk. You should not breast-feed during treatment with ARRANON.

- 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.

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 intravenous medicine. This means it is given through a tube in your vein.

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

These are not all the side effects associated 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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Research Triangle Park, NC 27709

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