

## 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/m<sup>2</sup> administered intravenously over 2 hours on days 1, 3, and 5 repeated every 21 days. (2.1)
- Pediatric dose: 650 mg/m<sup>2</sup> 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](http://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\*

### WARNING: NEUROLOGIC ADVERSE REACTIONS

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dosage
- 2.2 Dosage Modification
- 2.3 Adjustment of Dose in Special Populations
- 2.4 Prevention of Hyperuricemia
- 2.5 Instructions for Handling, Preparation, and Administration

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

- 5.1 Neurologic Adverse Reactions
- 5.2 Hematologic Adverse Reactions
- 5.3 Pregnancy
- 5.4 Hyperuricemia
- 5.5 Vaccinations

#### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

#### 7 DRUG INTERACTIONS

#### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

#### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### 14 CLINICAL STUDIES

- 14.1 Adult Clinical Study
- 14.2 Pediatric Clinical Study

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

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

1

2 **FULL PRESCRIBING INFORMATION**

3 **WARNING: NEUROLOGIC ADVERSE REACTIONS**

4 Severe neurologic adverse reactions have been reported with the use of ARRANON.  
5 These adverse reactions have included altered mental states including severe somnolence, central  
6 nervous system effects including convulsions, and peripheral neuropathy ranging from numbness  
7 and paresthesias to motor weakness and paralysis. There have also been reports of adverse  
8 reactions associated with demyelination, and ascending peripheral neuropathies similar in  
9 appearance to Guillain-Barré syndrome [see Warnings and Precautions (5.1)].

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

14 **1 INDICATIONS AND USAGE**

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

20 **2 DOSAGE AND ADMINISTRATION**

21 **2.1 Recommended Dosage**

22 This product is for intravenous use only.

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

28 Adult Dosage: The recommended adult dose of ARRANON is 1,500 mg/m<sup>2</sup>  
29 administered intravenously over 2 hours on days 1, 3, and 5 repeated every 21 days. ARRANON  
30 is administered undiluted.

31 Pediatric Dosage: The recommended pediatric dose of ARRANON is 650 mg/m<sup>2</sup>  
32 administered intravenously over 1 hour daily for 5 consecutive days repeated every 21 days.  
33 ARRANON is administered undiluted.

34 **2.2 Dosage Modification**

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

38 **2.3 Adjustment of Dose in Special Populations**

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

43 **2.4 Prevention of Hyperuricemia**

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

46 **2.5 Instructions for Handling, Preparation, and Administration**

47 Handling: ARRANON is a cytotoxic agent. Caution should be used during handling and  
48 preparation. Use of gloves and other protective clothing to prevent skin contact is recommended.  
49 Proper aseptic technique should be used. Guidelines for proper handling and disposal of  
50 anticancer drugs have been published.<sup>1-4</sup>

51 Preparation and Administration: Do not dilute ARRANON prior to administration.

52 The appropriate dose of ARRANON is transferred into polyvinylchloride (PVC) infusion bags or  
53 glass containers and administered as a two-hour infusion in adult patients and as a one-hour  
54 infusion in pediatric patients.

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

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

59 **3 DOSAGE FORMS AND STRENGTHS**

60 250 mg/50 mL (5 mg/mL) vial

61 **4 CONTRAINDICATIONS**

62 None.

63 **5 WARNINGS AND PRECAUTIONS**

64 **5.1 Neurologic Adverse Reactions**

65 Neurotoxicity is the dose-limiting toxicity of nelarabine. Patients undergoing therapy  
66 with ARRANON should be closely observed for signs and symptoms of neurologic toxicity [see  
67 *Boxed Warning and Dosage and Administration (2.2)*]. Common signs and symptoms of  
68 nelarabine-related neurotoxicity include somnolence, confusion, convulsions, ataxia,  
69 paresthesias, and hypoesthesia. Severe neurologic toxicity can manifest as coma, status  
70 epilepticus, craniospinal demyelination, or ascending neuropathy similar in presentation to  
71 Guillain-Barré syndrome.

72 Patients treated previously or concurrently with intrathecal chemotherapy or previously  
73 with craniospinal irradiation may be at increased risk for neurologic adverse events.

## 74 **5.2 Hematologic Adverse Reactions**

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

## 78 **5.3 Pregnancy**

79 Pregnancy Category D

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

81 Nelarabine administered during the period of organogenesis caused increased incidences  
82 of fetal malformations, anomalies, and variations in rabbits (*see Use in Specific Populations*  
83 *(8.1)*).

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

## 88 **5.4 Hyperuricemia**

89 Patients receiving ARRANON should receive intravenous hydration according to  
90 standard medical practice for the management of hyperuricemia in patients at risk for tumor lysis  
91 syndrome. Consideration should be given to the use of allopurinol in patients at risk of  
92 hyperuricemia [*see Dosage and Administration (2.4)*].

## 93 **5.5 Vaccinations**

94 Administration of live vaccines to immunocompromised patients should be avoided.

## 95 **6 ADVERSE REACTIONS**

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

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

## 101 **6.1 Clinical Trials Experience**

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

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

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

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

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

117

118 **Table 1. Most Commonly Reported ( $\geq 5\%$  Overall) Adverse Reactions Regardless of**  
 119 **Causality in Adult Patients Treated with 1,500 mg/m<sup>2</sup> of ARRANON Administered**  
 120 **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 <sup>a</sup> %	All Grades %
<b>Blood and Lymphatic System Disorders</b>			
Anemia	20	14	99
Thrombocytopenia	37	22	86
Neutropenia	14	49	81
Febrile neutropenia	9	1	12
<b>Cardiac Disorders</b>			
Sinus tachycardia	1	0	8
<b>Gastrointestinal Disorders</b>			
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
<b>General Disorders and Administration Site Conditions</b>			
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 <sup>a</sup> %	All Grades %
Chest pain	0	0	5
Non-cardiac chest pain	0	1	5
<b>Infections</b>			
Infection	2	1	9
Pneumonia	4	1	8
Sinusitis	1	0	7
<b>Hepatobiliary Disorders</b>			
AST increased	1	1	6
<b>Metabolism and Nutrition Disorders</b>			
Anorexia	0	0	9
Dehydration	3	1	7
Hyperglycemia	1	0	6
<b>Musculoskeletal and Connective Tissue Disorders</b>			
Myalgia	1	0	13
Arthralgia	1	0	9
Back pain	0	0	8
Muscular weakness	5	0	8
Pain in extremity	1	0	7
<b>Nervous System Disorders (see Table 2)</b>			
<b>Psychiatric Disorders</b>			
Confusional state	2	0	8
Insomnia	0	0	7
Depression	1	0	6
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>			
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
<b>Vascular Disorders</b>			
Petechiae	2	0	12
Hypotension	1	1	8

121 <sup>a</sup> Five patients had a fatal adverse reaction. Fatal adverse reactions included hypotension (n = 1),  
 122 respiratory arrest (n = 1), pleural effusion/pneumothorax (n = 1), pneumonia (n = 1), and cerebral  
 123 hemorrhage/coma/leukoencephalopathy (n = 1).  
 124

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

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

128 *Neurologic Adverse Reactions:* Nervous system adverse reactions, regardless of  
 129 drug relationship, were reported for 76% of adult patients across the Phase I and Phase II studies.  
 130 The most common neurologic adverse reactions ( $\geq 2\%$ ) in adult patients, regardless of causality,  
 131 including all grades (NCI Common Toxicity Criteria) are shown in Table 2.  
 132

133 **Table 2. Neurologic Adverse Reactions ( $\geq 2\%$ ) Regardless of Causality in Adult Patients**  
 134 **Treated with 1,500 mg/m<sup>2</sup> of ARRANON Administered Intravenously Over 2 Hours on**  
 135 **Days 1, 3, and 5 Repeated Every 21 Days**

Nervous System Disorders Preferred Term	Percentage of Patients (N =103)				
	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

136 One patient had a fatal neurologic adverse reaction, cerebral hemorrhage/coma/leukoencephalopathy.  
 137

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

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

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

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

156 The most common adverse reactions in pediatric patients, by System Organ Class,  
157 regardless of causality, including severe or life threatening adverse reactions (NCI Common  
158 Toxicity Criteria grade 3 or grade 4) and fatal adverse reactions (grade 5) are shown in Table 3.  
159

160 **Table 3. Most Commonly Reported ( $\geq 5\%$  Overall) Adverse Reactions Regardless of**  
 161 **Causality in Pediatric Patients Treated with 650 mg/m<sup>2</sup> of ARRANON Administered**  
 162 **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 <sup>a</sup> %	All Grades %
<b>Blood and Lymphatic System Disorders</b>			
Anemia	45	10	95
Neutropenia	17	62	94
Thrombocytopenia	27	32	88
Leukopenia	14	7	38
<b>Hepatobiliary Disorders</b>			
Transaminases increased	4	0	12
Blood albumin decreased	5	1	10
Blood bilirubin increased	7	2	10
<b>Metabolic/Laboratory</b>			
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
<b>Nervous System Disorders (see Table 4)</b>			
<b>Gastrointestinal Disorders</b>			
Vomiting	0	0	10
<b>General Disorders &amp; Administration Site Conditions</b>			
Asthenia	1	0	6
<b>Infections &amp; Infestations</b>			
Infection	2	1	5

163 <sup>a</sup> Three patients had a fatal adverse reaction. Fatal adverse reactions included neutropenia and pyrexia  
 164 (n = 1), status epilepticus/seizure (n = 1), and fungal pneumonia (n = 1).  
 165

166 *Neurologic Adverse Reactions:* Nervous system adverse reactions, regardless of  
 167 drug relationship, were reported for 42% of pediatric patients across the Phase I and Phase II  
 168 studies. The most common neurologic adverse reactions ( $\geq 2\%$ ) in pediatric patients, regardless  
 169 of causality, including all grades (NCI Common Toxicity Criteria) are shown in Table 4.  
 170

171 **Table 4. Neurologic Adverse Reactions ( $\geq 2\%$ ) Regardless of Causality in Pediatric Patients**  
 172 **Treated with 650 mg/m<sup>2</sup> of ARRANON Administered Intravenously Over 1 Hour Daily for**  
 173 **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 <sup>a</sup> %	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

174 <sup>a</sup> One (1) patient had a fatal neurologic adverse reaction, status epilepticus.  
 175

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

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

## 183 **6.2 Postmarketing Experience**

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

188 Infections and Infestations: Fatal opportunistic infections.

189 Metabolism and Nutrition Disorders: Tumor lysis syndrome.  
190 Nervous System Disorders: Demyelination and ascending peripheral neuropathies  
191 similar in appearance to Guillain-Barré syndrome.

## 192 **7 DRUG INTERACTIONS**

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

## 195 **8 USE IN SPECIFIC POPULATIONS**

### 196 **8.1 Pregnancy**

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

198 ARRANON can cause fetal harm when administered to a pregnant woman. Nelarabine  
199 administered to rabbits during the period of organogenesis caused increased incidences of fetal  
200 malformations, anomalies, and variations at doses  $\geq 360$  mg/m<sup>2</sup>/day (8-hour IV infusion;  
201 approximately ¼ the adult dose compared on a mg/m<sup>2</sup> basis), which was the lowest dose tested.  
202 Cleft palate was seen in rabbits given 3,600 mg/m<sup>2</sup>/day (approximately 2-fold the adult dose),  
203 absent pollices (digits) in rabbits given  $\geq 1,200$  mg/m<sup>2</sup>/day (approximately ¾ the adult dose),  
204 while absent gall bladder, absent accessory lung lobes, fused or extra sternbrae and delayed  
205 ossification was seen at all doses. Maternal body weight gain and fetal body weights were  
206 reduced in rabbits given 3,600 mg/m<sup>2</sup>/day (approximately 2-fold the adult dose), but could not  
207 account for the increased incidence of malformations seen at this or lower administered doses.

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

### 212 **8.3 Nursing Mothers**

213 It is not known whether nelarabine or ara-G are excreted in human milk. Because many  
214 drugs are excreted in human milk and because of the potential for serious adverse reactions in  
215 nursing infants from ARRANON, a decision should be made whether to discontinue nursing or  
216 to discontinue the drug, taking into account the importance of the drug to the mother.

### 217 **8.4 Pediatric Use**

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

### 220 **8.5 Geriatric Use**

221 Clinical studies of ARRANON did not include sufficient numbers of patients aged 65 and  
222 over to determine whether they respond differently from younger patients. In an exploratory  
223 analysis, increasing age, especially age 65 years and older, appeared to be associated with  
224 increased rates of neurologic adverse reactions. Because elderly patients are more likely to have  
225 decreased renal function, care should be taken in dose selection, and it may be useful to monitor  
226 renal function.

227 **8.6 Renal Impairment**

228 Ara-G clearance decreased as renal function decreased [see *Clinical Pharmacology*  
229 (12.3)]. Because the risk of adverse reactions to this drug may be greater in patients with  
230 moderate ( $CL_{cr}$  30 to 50 mL/min) or severe ( $CL_{cr}$  <30 mL/min) renal impairment, these patients  
231 should be closely monitored for toxicities when treated with ARRANON [see *Dosage and*  
232 *Administration* (2.3)].

233 **8.7 Hepatic Impairment**

234 The influence of hepatic impairment on the pharmacokinetics of nelarabine has not been  
235 evaluated. Because the risk of adverse reactions to this drug may be greater in patients with  
236 severe hepatic impairment (total bilirubin >3 times upper limit of normal), these patients should  
237 be closely monitored for toxicities when treated with ARRANON.

238 **10 OVERDOSAGE**

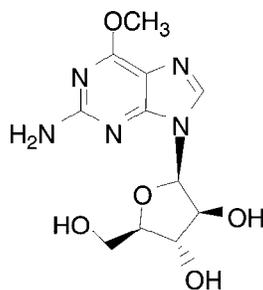
239 There is no known antidote for overdoses of ARRANON. It is anticipated that  
240 overdosage would result in severe neurotoxicity (possibly including paralysis, coma),  
241 myelosuppression, and potentially death. In the event of overdose, supportive care consistent  
242 with good clinical practice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

243 Nelarabine has been administered in clinical trials up to a dose of 2,900 mg/m<sup>2</sup> on days 1,  
244 3, and 5 to 2 adult patients. At a dose of 2,200 mg/m<sup>2</sup> given on days 1, 3, and 5 every 21 days, 2  
245 patients developed a significant grade 3 ascending sensory neuropathy. MRI evaluations of the 2  
246 patients demonstrated findings consistent with a demyelinating process in the cervical spine.

247 **11 DESCRIPTION**

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

250 The chemical name for nelarabine is 2-amino-9-β-D-arabinofuranosyl-6-methoxy-9H-  
251 purine. It has the molecular formula C<sub>11</sub>H<sub>15</sub>N<sub>5</sub>O<sub>5</sub> and a molecular weight of 297.27. Nelarabine  
252 has the following structural formula:



253  
254 Nelarabine is slightly soluble to soluble in water and melts with decomposition between  
255 209° and 217° C.

256 ARRANON Injection is supplied as a clear, colorless, sterile solution in glass vials. Each  
257 vial contains 250 mg of nelarabine (5 mg nelarabine per mL) and the inactive ingredient sodium

258 chloride (4.5 mg per mL) in 50 mL Water for Injection, USP. ARRANON is intended for  
259 intravenous infusion.

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

## 262 **12 CLINICAL PHARMACOLOGY**

### 263 **12.1 Mechanism of Action**

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

### 271 **12.3 Pharmacokinetics**

272 **Absorption:** Following intravenous administration of nelarabine to adult patients with  
273 refractory leukemia or lymphoma, plasma ara-G  $C_{max}$  values generally occurred at the end of the  
274 nelarabine infusion and were generally higher than nelarabine  $C_{max}$  values, suggesting rapid and  
275 extensive conversion of nelarabine to ara-G. Mean plasma nelarabine and ara-G  $C_{max}$  values  
276 were  $5.0 \pm 3.0$  µg/mL and  $31.4 \pm 5.6$  µg/mL, respectively, after a  $1,500$  mg/m<sup>2</sup> nelarabine dose  
277 infused over 2 hours in adult patients. The area under the concentration-time curve (AUC) of ara-  
278 G is 37 times higher than that for nelarabine on Day 1 after nelarabine IV infusion of  
279  $1,500$  mg/m<sup>2</sup> dose ( $162 \pm 49$  µg.h/mL versus  $4.4 \pm 2.2$  µg.h/mL, respectively). Comparable  $C_{max}$   
280 and AUC values were obtained for nelarabine between Days 1 and 5 at the nelarabine adult  
281 dosage of  $1,500$  mg/m<sup>2</sup>, indicating that nelarabine does not accumulate after multiple-dosing.  
282 There are not enough ara-G data to make a comparison between Day 1 and Day 5. After a  
283 nelarabine adult dose of  $1,500$  mg/m<sup>2</sup>, intracellular  $C_{max}$  for ara-GTP appeared within 3 to  
284 25 hours on Day 1. Exposure (AUC) to intracellular ara-GTP was 532 times higher than that for  
285 nelarabine and 14 times higher than that for ara-G ( $2,339 \pm 2,628$  µg.h/mL versus  
286  $4.4 \pm 2.2$  µg.h/mL and  $162 \pm 49$  µg.h/mL, respectively). Because the intracellular levels of ara-  
287 GTP were so prolonged, its elimination half-life could not be accurately estimated.

288 **Distribution:** Nelarabine and ara-G are extensively distributed throughout the body. For  
289 nelarabine,  $V_{SS}$  values were  $197 \pm 216$  L/m<sup>2</sup> in adult patients. For ara-G,  $V_{SS}/F$  values were  
290  $50 \pm 24$  L/m<sup>2</sup> in adult patients.

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

293 **Metabolism:** The principal route of metabolism for nelarabine is O-demethylation by  
294 adenosine deaminase to form ara-G, which undergoes hydrolysis to form guanine. In addition,  
295 some nelarabine is hydrolyzed to form methylguanine, which is O-demethylated to form  
296 guanine. Guanine is N-deaminated to form xanthine, which is further oxidized to yield uric acid.

297 **Excretion:** Nelarabine and ara-G are partially eliminated by the kidneys. Mean urinary  
298 excretion of nelarabine and ara-G was  $6.6 \pm 4.7\%$  and  $27 \pm 15\%$  of the administered dose,  
299 respectively, in 28 adult patients over the 24 hours after nelarabine infusion on Day 1. Renal  
300 clearance averaged  $24 \pm 23$  L/h for nelarabine and  $6.2 \pm 5.0$  L/h for ara-G in 21 adult patients.  
301 Combined Phase 1 pharmacokinetic data at nelarabine doses of 199 to 2,900 mg/m<sup>2</sup> (n = 66 adult  
302 patients) indicate that the mean clearance (CL) of nelarabine is  $197 \pm 189$  L/h/m<sup>2</sup> on Day 1. The  
303 apparent clearance of ara-G (CL/F) is  $10.5 \pm 4.5$  L/h/m<sup>2</sup> on Day 1. Nelarabine and ara-G are  
304 rapidly eliminated from plasma with a mean half-life of 18 minutes and 3.2 hours, respectively,  
305 in adult patients.

306 **Pediatrics:** No pharmacokinetic data are available in pediatric patients at the once daily  
307 650 mg/m<sup>2</sup> nelarabine dosage. Combined Phase 1 pharmacokinetic data at nelarabine doses of  
308 104 to 2,900 mg/m<sup>2</sup> indicate that the mean clearance (CL) of nelarabine is about 30% higher in  
309 pediatric patients than in adult patients ( $259 \pm 409$  L/h/m<sup>2</sup> versus  $197 \pm 189$  L/h/m<sup>2</sup>, respectively)  
310 (n = 66 adults, n = 22 pediatric patients) on Day 1. The apparent clearance of ara-G (CL/F) is  
311 comparable between the two groups ( $10.5 \pm 4.5$  L/h/m<sup>2</sup> in adult patients and  $11.3 \pm 4.2$  L/h/m<sup>2</sup> in  
312 pediatric patients) on Day 1. Nelarabine and ara-G are extensively distributed throughout the  
313 body. For nelarabine, V<sub>SS</sub> values were  $213 \pm 358$  L/m<sup>2</sup> in pediatric patients. For ara-G,  
314 V<sub>SS</sub>/F values were  $33 \pm 9.3$  L/m<sup>2</sup> in pediatric patients. Nelarabine and ara-G are rapidly  
315 eliminated from plasma in pediatric patients, with a half-life of 13 minutes and 2 hours,  
316 respectively.

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

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

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

326 **Effect of Renal Impairment:** The pharmacokinetics of nelarabine and ara-G have not  
327 been specifically studied in renally impaired or hemodialyzed patients. Nelarabine is excreted by  
328 the kidney to a small extent (5 to 10% of the administered dose). Ara-G is excreted by the kidney  
329 to a greater extent (20 to 30% of the administered nelarabine dose). In the combined Phase 1  
330 studies, patients were categorized into 3 groups: normal with CL<sub>cr</sub> >80 mL/min (n = 67), mild  
331 with CL<sub>cr</sub> = 50-80 mL/min (n = 15), and moderate with CL<sub>cr</sub> <50 mL/min (n = 3). The mean  
332 apparent clearance (CL/F) of ara-G was about 15% and 40% lower in patients with mild and  
333 moderate renal impairment, respectively, than in patients with normal renal function [*see Use in*  
334 *Specific Populations (8.6) and Dosage and Administration (2.3)*]. No differences in safety or  
335 effectiveness were observed.

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

338 Drug Interactions: Cytochrome P450: Nelarabine and ara-G did not significantly  
339 inhibit the activities of the human hepatic cytochrome P450 isoenzymes 1A2, 2A6, 2B6, 2C8,  
340 2C9, 2C19, 2D6, or 3A4 in vitro at concentrations of nelarabine and ara-G up to 100 µM.

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

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

## 349 **13 NONCLINICAL TOXICOLOGY**

### 350 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

## 355 **14 CLINICAL STUDIES**

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

### 358 **14.1 Adult Clinical Study**

359 The safety and efficacy of ARRANON in adult patients were studied in a clinical trial  
360 which included 39 treated patients, 28 who had T-cell acute lymphoblastic leukemia (T-ALL) or  
361 T-cell lymphoblastic lymphoma (T-LBL) that had relapsed following or was refractory to at least  
362 two prior induction regimens. A 1,500 mg/m<sup>2</sup> dose of ARRANON was administered  
363 intravenously over 2 hours on days 1, 3, and 5 repeated every 21 days. Patients who experienced  
364 signs or symptoms of grade 2 or greater neurologic toxicity on therapy were to be discontinued  
365 from further therapy with ARRANON. Seventeen patients had a diagnosis of T-ALL and 11 had  
366 a diagnosis of T-LBL. For patients with ≥2 prior inductions, the age range was 16-65 years  
367 (mean 34 years) and most patients were male (82%) and Caucasian (61%). Patients with central  
368 nervous system (CNS) disease were not eligible.

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

373

374 **Table 5. Efficacy Results in Adult Patients With  $\geq 2$  Prior Inductions Treated with**  
 375 **1,500 mg/m<sup>2</sup> of ARRANON Administered Intravenously Over 2 Hours on Days 1, 3, and 5**  
 376 **Repeated Every 21 Days**

	<b>N = 28</b>
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) <sup>a</sup>	4 to 195+
Median overall survival (weeks) [95% CI]	20.6 weeks [10.4, 36.4]

377 CR = Complete response

378 CR\* = Complete response without hematologic recovery

379 <sup>a</sup> Does not include 1 patient who was transplanted (duration of response was 156+ weeks).

380

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

### 383 **14.2 Pediatric Clinical Study**

384 The safety and efficacy of ARRANON in pediatric patients were studied in a clinical trial  
 385 which included patients 21 years of age and younger, who had relapsed or refractory T-cell acute  
 386 lymphoblastic leukemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LBL). Eighty-four (84)  
 387 patients, 39 of whom had received two or more prior induction regimens, were treated with  
 388 650 mg/m<sup>2</sup>/day of ARRANON administered intravenously over 1 hour daily for 5 consecutive  
 389 days repeated every 21 days (see Table 6). Patients who experienced signs or symptoms of grade  
 390 2 or greater neurologic toxicity on therapy were to be discontinued from further therapy with  
 391 ARRANON.

392

393 **Table 6. Pediatric Clinical Study - Patient Allocation**

<b>Patient Population</b>	<b>N</b>
Patients treated at 650 mg/m <sup>2</sup> /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 <sup>2</sup> /day x 5 days every 21 days.	39
Patients with T-ALL or T-LBL with one prior induction treated at 650 mg/m <sup>2</sup> /day x 5 days every 21 days.	31

394

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

398 Complete response (CR) in this study was defined as bone marrow blast counts  $\leq 5\%$ , no  
 399 other evidence of disease, and full recovery of peripheral blood counts. Complete response  
 400 without full hematologic recovery (CR\*) was also assessed as a meaningful outcome in this  
 401 heavily pretreated population. Duration of response is reported from date of response to date of

402 relapse, and may include subsequent stem cell transplant. Efficacy results are presented in  
403 Table 7.

404  
405 **Table 7. Efficacy Results in Patients 21 Years of Age and Younger at Diagnosis With  $\geq 2$**   
406 **Prior Inductions Treated with 650 mg/m<sup>2</sup> of ARRANON Administered Intravenously Over**  
407 **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) <sup>a</sup>	3.3 to 9.3
Median overall survival (weeks) [95% CI]	13.1 [8.7, 17.4]

408 CR = Complete response

409 CR\* = Complete response without hematologic recovery

410 <sup>a</sup> Does not include 5 patients who were transplanted or had subsequent systemic chemotherapy  
411 (duration of response in these 5 patients was 4.7 to 42.1 weeks).

412  
413 The mean number of days on therapy was 46 days (range of 7 to 129 days). Median time  
414 to CR plus CR\* was 3.4 weeks (95% CI: 3.0, 3.7).

## 415 15 REFERENCES

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## 425 16 HOW SUPPLIED/STORAGE AND HANDLING

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

431 NDC 0007-4401-06 (package of 6)

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

434 **17 PATIENT COUNSELING INFORMATION**

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

- 437 • Since patients receiving nelarabine therapy may experience somnolence, they should be  
438 cautioned about operating hazardous machinery, including automobiles.
- 439 • Patients should be instructed to contact their physician if they experience new or worsening  
440 symptoms of peripheral neuropathy (*see Boxed Warning, Warnings and Precautions (5.1), and*  
441 *Dosage and Administration (2.3)*). These signs and symptoms include: tingling or numbness in  
442 fingers, hands, toes, or feet; difficulty with the fine motor coordination tasks such as buttoning  
443 clothing; unsteadiness while walking; weakness arising from a low chair; weakness in climbing  
444 stairs; increased tripping while walking over uneven surfaces.
- 445 • Patients should be instructed that seizures have been known to occur in patients who receive  
446 nelarabine. If a seizure occurs, the physician administering ARRANON should be promptly  
447 informed.
- 448 • Patients who develop fever or signs of infection while on therapy should notify their  
449 physician promptly.
- 450 • Patients should be advised to use effective contraceptive measures to prevent pregnancy and  
451 to avoid breast-feeding during treatment with ARRANON.

452  
453 ARRANON is a registered trademark of GlaxoSmithKline.  
454



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456 GlaxoSmithKline  
457 Research Triangle Park, NC 27709  
458

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460

461 PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

462 -----  
463 **PATIENT INFORMATION LEAFLET**  
464 **ARRANON<sup>®</sup> (AIR-ra-non)**  
465 **Nelarabine Injection**  
466

467 Read the Patient Information that comes with ARRANON before you or your child start  
468 treatment with ARRANON. Read the information you get each time before each treatment with  
469 ARRANON. There may be new information. This information does not take the place of talking  
470 with the doctor about your or your child's medical condition or treatment. Talk to your or your  
471 child's doctor, if you have any questions.  
472

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

474 **ARRANON may cause serious nervous system problems including:**

- 475
- 476 • extreme sleepiness
  - 477 • seizures
  - 478 • coma
  - 479 • numbness and tingling in the hands, fingers, feet, or toes (peripheral neuropathy)
  - 480 • weakness and paralysis

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

- 482
- 483 • seizures
  - 484 • numbness and tingling in the hands, fingers, feet, or toes
  - 485 • problems with fine motor skills such as buttoning clothes
  - 486 • unsteadiness while walking
  - 487 • increased tripping while walking
  - 488 • weakness when getting out of a chair or walking up stairs

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

490

491 **What is ARRANON?**

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

- 493
- 494 • T-cell acute lymphoblastic leukemia
  - 495 • T-cell lymphoblastic lymphoma

496 **What should you tell the doctor before you or your child starts ARRANON?**

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

- 498
- 499 • have any nervous system problems.
  - 500 • have kidney problems.
  - 501 • 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.

- 502 • are pregnant or plan to become pregnant. ARRANON may harm an unborn baby. You should  
503 use effective birth control to avoid getting pregnant. Talk with your doctor about your  
504 choices.  
505

506 Tell the doctor about all the medicines you or your child take, including prescription and  
507 nonprescription medicines, vitamins, and herbal supplements.  
508

509 **How is ARRANON given?**

510 ARRANON is an intravenous medicine. This means it is given through a tube in your vein.  
511

512 **What should you or your child avoid during treatment with ARRANON?**

- 513 • You or your child should not drive or operate dangerous machines. ARRANON may cause  
514 sleepiness.  
515 • You or your child should not receive vaccines made with live germs during treatment with  
516 ARRANON.  
517

518 **What are the possible side effects of ARRANON?**

519 **ARRANON may cause serious nervous system problems.** See “What is the most important  
520 information I should know about ARRANON?”  
521

522 **ARRANON may also cause:**

- 523 • decreased blood counts such as low red blood cells, low white blood cells, and low platelets.  
524 Blood tests should be done regularly to check blood counts. Call the doctor right away if you  
525 or your child:  
526 • is more tired than usual, pale, or has trouble breathing  
527 • has a fever or other signs of an infection  
528 • bruises easy or has any unusual bleeding  
529 • stomach area problems such as nausea, vomiting, diarrhea, and constipation  
530 • headache  
531 • sleepiness  
532 • blurry eyesight  
533

534 These are not all the side effects associated with ARRANON. Ask your doctor or pharmacist for  
535 more information.  
536

537 **General Advice about ARRANON**

538 This leaflet summarizes important information about ARRANON. If you have questions or  
539 problems, talk with your or your child’s doctor. You can ask your doctor or pharmacist for  
540 information about ARRANON that is written for healthcare providers or it is available at  
541 [www.GSK.com](http://www.GSK.com).  
542

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544



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