

NDA 021877/S-005

Page 1

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)

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

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: December 2011

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 **FULL PRESCRIBING INFORMATION**

2 **WARNING: NEUROLOGIC ADVERSE REACTIONS**

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

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

13 **1 INDICATIONS AND USAGE**

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

19 **2 DOSAGE AND ADMINISTRATION**

20 **2.1 Recommended Dosage**

21 This product is for intravenous use only.

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

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

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

33 **2.2 Dosage Modification**

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

37 **2.3 Adjustment of Dose in Special Populations**

38 ARRANON has not been studied in patients with renal or hepatic dysfunction [see Use in
39 *Specific Populations* (8.6, 8.7)]. No dose adjustment is recommended for patients with a

40 creatinine clearance (CL_{cr}) ≥ 50 mL/min [see *Clinical Pharmacology (12.3)*]. There are
41 insufficient data to support a dose recommendation for patients with a $CL_{cr} < 50$ mL/min.

42 **2.4 Prevention of Hyperuricemia**

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

45 **2.5 Instructions for Handling, Preparation, and Administration**

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

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

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

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

58 **3 DOSAGE FORMS AND STRENGTHS**

59 250 mg/50 mL (5 mg/mL) vial

60 **4 CONTRAINDICATIONS**

61 None.

62 **5 WARNINGS AND PRECAUTIONS**

63 **5.1 Neurologic Adverse Reactions**

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

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

73 **5.2 Hematologic Adverse Reactions**

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

77 **5.3 Pregnancy**

78 Pregnancy Category D

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

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

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

87 **5.4 Hyperuricemia**

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

92 **5.5 Vaccinations**

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

94 **6 ADVERSE REACTIONS**

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

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

100 **6.1 Clinical Trials Experience**

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

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

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

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

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

116

117 **Table 1. Most Commonly Reported (≥5% Overall) Adverse Reactions Regardless of**
 118 **Causality in Adult Patients Treated with 1,500 mg/m² of ARRANON Administered**
 119 **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
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

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

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

124 *Other Adverse Events:* Blurred vision was also reported in 4% of adult patients.
125 There was a single report of biopsy confirmed progressive multifocal
126 leukoencephalopathy in the adult patient population.

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

132 **Table 2. Neurologic Adverse Reactions (≥2%) Regardless of Causality in Adult Patients**
 133 **Treated with 1,500 mg/m² of ARRANON Administered Intravenously Over 2 Hours on**
 134 **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

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

136

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

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

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

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

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

159 **Table 3. Most Commonly Reported (≥5% Overall) Adverse Reactions Regardless of**
160 **Causality in Pediatric Patients Treated with 650 mg/m² of ARRANON Administered**
161 **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

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

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

170 **Table 4. Neurologic Adverse Reactions (≥2%) Regardless of Causality in Pediatric Patients**
 171 **Treated with 650 mg/m² of ARRANON Administered Intravenously Over 1 Hour Daily for**
 172 **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

173 ^a One (1) patient had a fatal neurologic adverse reaction, status epilepticus.

174
 175 The other grade 3 neurologic adverse reaction in pediatric patients, regardless of
 176 causality, was hypertonia reported in 1 patient (1%). The additional grade 4 neurologic adverse
 177 reactions, regardless of causality, were 3rd nerve paralysis, and 6th nerve paralysis, each reported
 178 in 1 patient (1%).

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

182 **6.2 Postmarketing Experience**

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

187 Infections and Infestations: Fatal opportunistic infections.

188 Metabolism and Nutrition Disorders: Tumor lysis syndrome.

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

191 Musculoskeletal and Connective Disorders: Rhabdomyolysis, blood creatine
 192 phosphokinase increased.

193 **7 DRUG INTERACTIONS**

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

196 **8 USE IN SPECIFIC POPULATIONS**

197 **8.1 Pregnancy**

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

199 ARRANON can cause fetal harm when administered to a pregnant woman. Nelarabine
200 administered to rabbits during the period of organogenesis caused increased incidences of fetal
201 malformations, anomalies, and variations at doses ≥ 360 mg/m²/day (8-hour IV infusion;
202 approximately $\frac{1}{4}$ the adult dose compared on a mg/m² basis), which was the lowest dose tested.
203 Cleft palate was seen in rabbits given 3,600 mg/m²/day (approximately 2-fold the adult dose),
204 absent pollices (digits) in rabbits given $\geq 1,200$ mg/m²/day (approximately $\frac{3}{4}$ the adult dose),
205 while absent gall bladder, absent accessory lung lobes, fused or extra sternebrae and delayed
206 ossification was seen at all doses. Maternal body weight gain and fetal body weights were
207 reduced in rabbits given 3,600 mg/m²/day (approximately 2-fold the adult dose), but could not
208 account for the increased incidence of malformations seen at this or lower administered doses.

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

213 **8.3 Nursing Mothers**

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

218 **8.4 Pediatric Use**

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

221 **8.5 Geriatric Use**

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

228 **8.6 Renal Impairment**

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

234 **8.7 Hepatic Impairment**

235 The influence of hepatic impairment on the pharmacokinetics of nelarabine has not been
236 evaluated. Because the risk of adverse reactions to this drug may be greater in patients with

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

239 **10 OVERDOSAGE**

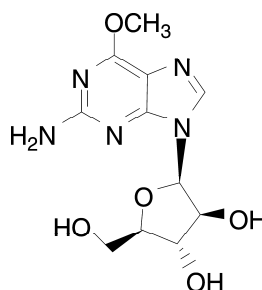
240 There is no known antidote for overdoses of ARRANON. It is anticipated that
241 overdosage would result in severe neurotoxicity (possibly including paralysis, coma),
242 myelosuppression, and potentially death. In the event of overdose, supportive care consistent
243 with good clinical practice should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

244 Nelarabine has been administered in clinical trials up to a dose of 2,900 mg/m² on days 1,
245 3, and 5 to 2 adult patients. At a dose of 2,200 mg/m² given on days 1, 3, and 5 every 21 days, 2
246 patients developed a significant grade 3 ascending sensory neuropathy. MRI evaluations of the 2
247 patients demonstrated findings consistent with a demyelinating process in the cervical spine.

248 **11 DESCRIPTION**

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

251 The chemical name for nelarabine is 2-amino-9-β-*D*-arabinofuranosyl-6-methoxy-9*H*-
252 purine. It has the molecular formula C₁₁H₁₅N₅O₅ and a molecular weight of 297.27. Nelarabine
253 has the following structural formula:



254

255 Nelarabine is slightly soluble to soluble in water and melts with decomposition between
256 209° and 217° C.

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

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

263 **12 CLINICAL PHARMACOLOGY**

264 **12.1 Mechanism of Action**

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

272 12.3 Pharmacokinetics

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

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

293 Nelarabine and ara-G are not substantially bound to human plasma proteins (<25%) in
294 vitro, and binding is independent of nelarabine or ara-G concentrations up to $600 \mu\text{M}$.

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

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

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

317 eliminated from plasma in pediatric patients, with a half-life of 13 minutes and 2 hours,
318 respectively.

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

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

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

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

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

340 Drug Interactions: Cytochrome P450: Nelarabine and ara-G did not significantly
341 inhibit the activities of the human hepatic cytochrome P450 isoenzymes 1A2, 2A6, 2B6, 2C8,
342 2C9, 2C19, 2D6, or 3A4 in vitro at concentrations of nelarabine and ara-G up to 100 μ M.

343 Fludarabine: Administration of fludarabine 30 mg/m² as a 30-minute infusion
344 4 hours before a 1,200 mg/m² infusion of nelarabine did not affect the pharmacokinetics of
345 nelarabine, ara-G, or ara-GTP in 12 patients with refractory leukemia.

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

351 **13 NONCLINICAL TOXICOLOGY**

352 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

357 **14 CLINICAL STUDIES**

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

360 **14.1 Adult Clinical Study**

361 The safety and efficacy of ARRANON in adult patients were studied in a clinical trial
362 which included 39 treated patients, 28 who had T-cell acute lymphoblastic leukemia (T-ALL) or
363 T-cell lymphoblastic lymphoma (T-LBL) that had relapsed following or was refractory to at least
364 two prior induction regimens. A 1,500 mg/m² dose of ARRANON was administered
365 intravenously over 2 hours on days 1, 3, and 5 repeated every 21 days. Patients who experienced
366 signs or symptoms of grade 2 or greater neurologic toxicity on therapy were to be discontinued
367 from further therapy with ARRANON. Seventeen patients had a diagnosis of T-ALL and 11 had
368 a diagnosis of T-LBL. For patients with ≥2 prior inductions, the age range was 16-65 years
369 (mean 34 years) and most patients were male (82%) and Caucasian (61%). Patients with central
370 nervous system (CNS) disease were not eligible.

371 Complete response (CR) in this study was defined as bone marrow blast counts ≤5%, no
372 other evidence of disease, and full recovery of peripheral blood counts. Complete response
373 without complete hematologic recovery (CR*) was also assessed. The results of the study for
374 patients who had received ≥2 prior inductions are shown in Table 5.
375

376 **Table 5. Efficacy Results in Adult Patients With ≥2 Prior Inductions Treated with**
377 **1,500 mg/m² of ARRANON Administered Intravenously Over 2 Hours on Days 1, 3, and 5**
378 **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]

379 CR = Complete response

380 CR* = Complete response without hematologic recovery

381 ^a Does not include 1 patient who was transplanted (duration of response was 156+ weeks).
382

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

385 **14.2 Pediatric Clinical Study**

386 The safety and efficacy of ARRANON in pediatric patients were studied in a clinical trial
387 which included patients 21 years of age and younger, who had relapsed or refractory T-cell acute
388 lymphoblastic leukemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LBL). Eighty-four (84)
389 patients, 39 of whom had received two or more prior induction regimens, were treated with
390 650 mg/m²/day of ARRANON administered intravenously over 1 hour daily for 5 consecutive
391 days repeated every 21 days (see Table 6). Patients who experienced signs or symptoms of grade
392 2 or greater neurologic toxicity on therapy were to be discontinued from further therapy with
393 ARRANON.
394

395 **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

396

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

400 Complete response (CR) in this study was defined as bone marrow blast counts ≤5%, no
401 other evidence of disease, and full recovery of peripheral blood counts. Complete response
402 without full hematologic recovery (CR*) was also assessed as a meaningful outcome in this
403 heavily pretreated population. Duration of response is reported from date of response to date of
404 relapse, and may include subsequent stem cell transplant. Efficacy results are presented in
405 Table 7.

406

407 **Table 7. Efficacy Results in Patients 21 Years of Age and Younger at Diagnosis With ≥2**
408 **Prior Inductions Treated with 650 mg/m² of ARRANON Administered Intravenously Over**
409 **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]

410 CR = Complete response

411 CR* = Complete response without hematologic recovery

412 ^a Does not include 5 patients who were transplanted or had subsequent systemic chemotherapy
413 (duration of response in these 5 patients was 4.7 to 42.1 weeks).

414

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

417 **15 REFERENCES**

- 418 1. Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health
419 Care Settings. NIOSH Alert 2004-165.
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422 http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
- 423 3. American Society of Health-System Pharmacists. ASHP Guidelines on Handling Hazardous
424 Drugs. *Am J Health-Syst Pharm.* 2006;63:1172-1193.

- 425 4. Polovich M, White JM, Kelleher LO (eds.) 2005. Chemotherapy and Biotherapy Guidelines
426 and Recommendations for Practice. (2nd ed) Pittsburgh, PA: Oncology Nursing Society.

427 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

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

436 **17 PATIENT COUNSELING INFORMATION**

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

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

454
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456



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458 GlaxoSmithKline
459 Research Triangle Park, NC 27709
460

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463 December 2011

NDA 021877/S-005
Page 17

464 ARR:2PI

465 PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

466

467

468

469

470

PATIENT INFORMATION LEAFLET

ARRANON[®] (AIR-ra-non)

Nelarabine Injection

471

472

473

474

475

476

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.

477

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

478

ARRANON may cause serious nervous system problems including:

479

- extreme sleepiness

480

- seizures

481

- coma

482

- numbness and tingling in the hands, fingers, feet, or toes (peripheral neuropathy)

483

- weakness and paralysis

484

485

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

486

- seizures

487

- numbness and tingling in the hands, fingers, feet, or toes

488

- problems with fine motor skills such as buttoning clothes

489

- unsteadiness while walking

490

- increased tripping while walking

491

- weakness when getting out of a chair or walking up stairs

492

493

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

494

495

What is ARRANON?

496

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

497

- T-cell acute lymphoblastic leukemia

498

- T-cell lymphoblastic lymphoma

499

500

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

501

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

502

- have any nervous system problems.

503

- have kidney problems.

504

- 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.

505

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

509

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

512

513 **How is ARRANON given?**

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

515

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

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

521

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

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

525

526 **ARRANON may also cause:**

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

537

538 Call your doctor right away if you experience unexplained muscle pain, tenderness, or weakness
539 while taking ARRANON. This is because on rare occasions, muscle problems can be serious.

540

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

543

544 **General Advice about ARRANON**

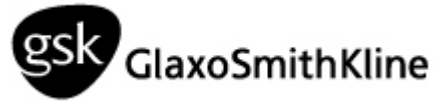
545 This leaflet summarizes important information about ARRANON. If you have questions or
546 problems, talk with your or your child’s doctor. You can ask your doctor or pharmacist for
547 information about ARRANON that is written for healthcare providers or it is available at
548 www.GSK.com.

549

NDA 021877/S-005

Page 20

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