ASADIN Injection 1 mg/ml

Arsenic Trioxide 1 mg/ml

WARNING: DIFFERENTIATION SYNDROME, CARDIAC CONDUCTION ABNORMALITIES AND ENCEPHALOPATHY INCLUDING WERNICKE'S

Differentiation Syndrome: Patients with acute promyelocytic leukemia (APL) treated with Arsenic Trioxide have experienced symptoms of differentiation syndrome, which may life-threatening or fatal. Signs and symptoms may include unexplained fever, dyspnea, hypoxia, acute respiratory distress, pulmonary infiltrates, pleural or pericardial effusions, weight gain, peripheral edema, hypotension, renal insufficiency, hepatopathy, and multi-organ dysfunction, in the presence or absence of leukocytosis. If differentiation syndrome is suspected, immediately initiate high-dose corticosteroids and hemodynamic monitoring until resolution. Temporarily withhold Arsenic Trioxide [see Dosage and Administration (2.3), Warnings and Precautions (5.1)].

Cardiac Conduction Abnormalities: Arsenic Trioxide can cause QTc interval prolongation, complete atrioventricular block, and torsade de pointes, which can be fatal. Before administering Arsenic Trioxide, assess the QTc interval, correct electrolyte abnormalities, and consider discontinuing drugs known to prolong QTc interval. Do not administer Arsenic Trioxide to patients with a ventricular arrhythmia or prolonged QTc interval. Withhold Arsenic Trioxide until resolution and resume at reduced dose for QTc prolongation [see Dosage and Administration (2.3), Warnings and Precautions (5.2)].

Encephalopathy: Serious encephalopathy, including Wernicke's, has occurred with Arsenic Trioxide. Wernicke's is a neurologic emergency. Consider testing thiamine levels in patients at risk for thiamine deficiency. Administer parenteral thiamine in patients with or at risk for thiamine deficiency. Monitor patients for neurological symptoms and nutritional status while receiving Arsenic Trioxide X. If Wernicke's encephalopathy is suspected, immediately interrupt Arsenic Trioxide and initiate parenteral thiamine. Monitor until symptoms resolve or improve and thiamine levels normalize [see Warnings and Precautions (5.3)].

1. INDICATIONS AND USAGE

1.1. Newly-Diagnosed Low-to-Intermediate-Risk Acute promyelocytic leukaemia

Arsenic Trioxide is indicated in combination with tretinoin for treatment of adults with newly-diagnosed low-to-intermediate risk acute promyelocytic leukemia (APL) whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression.

1.2. Relapsed or Refractory Acute promyelocytic leukaemia

For the induction of remission and consolidation in patients with acute promyelocytic leukaemia (APL) who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterised by the presence of the t(15:17) translocation or PML/RAR-alpha gene expression.

2. DOSAGE AND ADMINISTRATION

2.1. Recommended Dosage for Newly-Diagnosed Low-to-Intermediate-Risk Acute Promyelocytic Leukemia (APL)

A treatment course for patients with newly-diagnosed low-to-intermediate-risk APL consists of 1 induction cycle and 4 consolidation cycles.

- For the induction cycle, the recommended dosage of Arsenic Trioxide is 0.15 mg/kg intravenously daily in combination with tretinoin until bone marrow remission but not to exceed 60 days (see Table 1).
- For the consolidation cycles, the recommended dosage of Arsenic Trioxide is 0.15 mg/kg intravenously daily 5 days per week during weeks 1-4 of each 8-week cycle for a total of 4 cycles in

combination with tretinoin (see Table 1). Omit tretinoin during weeks 5-6 of the fourth cycle of consolidation.

Table 1 **Recommended Dose of ASADIN in Low-to-Intermediate-Risk Patients**

Induction (1 cycle)

Arsenic Trioxide 0.15 mg/kg once daily intravenously	Until marrow remission but not to exceed 60 days
Tretinoin[a] 22.5 mg/m^2 twice daily orally	Until marrow remission but not to exceed 60 days

Consolidation (4 cycles)

	Week							
	1	2	3	4	5	6	7	8
Arsenic Trioxide 0.15 mg/kg QD, iv	D[C] 1-5	D 1-5	D 1-5	D 1-5	--	--	--	--
Tretinoin[a] 22.5 mg/m^2 BID, po	D 1-7	D 1-7	--	--	D[b] 1-7	D[b] 1-7	--	--

[a]Rounded to the nearest 10 mg increment

[b]Omitted during the 4th cycle of consolidation

[C]D: Days

Differentiation syndrome prophylaxis consisting of prednisone 0.5 mg/kg daily from day 1 until the end of induction therapy with Arsenic Trioxide and tretinoin is recommended.

2.2 Recommended Dosage for Relapsed or Refractory APL

A treatment course for patients with relapsed or refractory APL consists of 1 induction cycle and 1 consolidation cycle [see Clinical Studies (14.2)].

- For the induction cycle, the recommended dosage of Arsenic Trioxide is 0.15 mg/kg/day intravenously daily until bone marrow remission or up to a maximum of 60 days.
- For the consolidation cycle, the recommended dosage of Arsenic Trioxide is 0.15 mg/kg/day intravenously daily for 25 doses over a period of up to 5 weeks. Begin consolidation 3 to 6 weeks after completion of induction cycle.

2.3 Monitoring and Dosage Modifications for Adverse Reactions

During induction, monitor coagulation studies, blood counts, and chemistries at least 2-3 times per week through recovery. During consolidation, monitor coagulation studies, blood counts, and chemistries at least weekly.

Table 2 shows the dose modifications for adverse reactions due to Arsenic Trioxide when used alone or in combination with tretinoin.

Table 2 **Dose Adjustments for Adverse Reactions of Arsenic Trioxide**

Adverse Reaction	Dose Modification
Differentiation syndrome, defined by the presence of 2 or more of the following: – Unexplained fever – Dyspnea – Pleural and/or pericardial effusion – Pulmonary infiltrates – Renal failure – Hypotension – Weight gain greater than 5 kg [see Warnings and Precautions (5.1)]	• Temporarily withhold ASADIN. Consider holding tretinoin if symptoms are severe. • Administer dexamethasone 10 mg intravenously every 12 hours until the resolution of signs and symptoms for a minimum of 3 days. • Resume treatment when the clinical condition improves and reduce the dose of the withheld drug(s) by 50%. • Increase the dose of the withheld drug(s) to the recommended dosage after one week in the absence of recurrence of symptoms of differentiation syndrome. • If symptoms re-appear, decrease ASADIN and/or tretinoin to the previous dose.

Adverse Reaction	Dose Modification
QTc (Framingham formula) Prolongation greater than 450 msec for men or greater than 460 msec for women [see Warnings and Precautions (5.2)]	• Withhold Arsenic Trioxide and any medication known to prolong the QTc interval. • Correct electrolyte abnormalities.. • After the QTc normalizes, and electrolyte abnormalities are corrected, resume treatment with ASADIN at a 50% reduced dose (0.075 mg/kg daily) for one week after resolution. • If the 50% reduced dose is tolerated for one week (in the absence of QTc prolongation), increase the dose of ASADIN to 0.11 mg/kg/day for the next week [see Dosage and Administration (2.1)]. • The dose of ASADIN can be increased to 0.15 mg/kg/day in the absence of QTc prolongation during that 14-day dose-escalation period.

Adverse Reaction	Dose Modification
Hepatotoxicity, defined by 1 or more of the following: – Total bilirubin (TB) greater than 3 times the upper limit of normal (ULN) – Aspartate aminotransferase (AST) greater than 5 times the ULN – Alkaline phosphatase (AP) greater than 5 times the ULN [see Warnings and Precautions (5.4)]	• Withhold ASADIN and/or tretinoin. • Resume treatment at a 50% reduced dose of the withheld drug(s) when TB is less than 1.5 times the ULN and AP/AST are less than 3 times the ULN • Increase the dose of the withheld drug(s) back to the recommended dosage after one week on the reduced dose in the absence of worsening of hepatotoxicity • Discontinue the withheld drug(s) permanently if hepatotoxicity recurs.
Other severe or life-threatening (grade 3-4) nonhematologic reactions [see Adverse Reactions (6)]	• Temporarily withhold ASADIN and tretinoin. • When the adverse reaction resolves to no more than mild (grade 1), resume ASADIN and tretinoin reduced by 2 dose levels (see Table 3 below).
Moderate (grade 2) nonhematologic reactions [see Adverse Reactions (6)]	• Reduce the dose of ASADIN and/or tretinoin by 1 dose level (see Table 3 below).
Leukocytosis (WBC count greater than 10 Gi/L) [see Adverse Reactions (6.1)]	• Administer hydroxyurea:. WBC / Hydroxyurea 10-50 Gi/L / 500 mg QID >50 Gi/L / 1000 mg QID • Hydroxyurea may be discontinued when the WBC declines below 10 Gi/L.
Myelosuppression, defined by 1 or more of the following: – absolute neutrophil count less than 1 Gi/L – platelets less than 50 Gi/L lasting more than 5 weeks [see Adverse Reactions (6)]	• Consider reducing the dose of ASADIN and tretinoin by 1 dose level (see Table 3 below). • If myelosuppression lasts ≥ 50 days or occurs on 2 consecutive cycles, assess a marrow aspirate for remission status. In the case of molecular remission, resume ASADIN and tretinoin at 1 dose level lower (see Table 3 below).

Table 3 **Dose Reduction Levels for Hematologic and Nonhematologic Toxicities**

Dose Level	Arsenic Trioxide mg/kg intravenously once daily	Tretinoin* mg/m^2 orally twice daily
Starting level	0.15	22.5
-1	0.11	18.75
-2	0.10	12.5
-3	0.075	10

*Rounded to the nearest 10 mg increment

2.4 Preparation and Administration

Reconstitution

Dilute ASADIN with 100 or 250 mL 5% Dextrose Injection, or 0.9% Sodium Chloride Injection, using proper aseptic technique, immediately after withdrawal from the vial.

After dilution, ASADIN is chemically and physically stable when stored for 24 hours at room temperature or 48 hours when refrigerated at 2-8℃.

Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Administer Arsenic Trioxide as an intravenous infusion over 2 hours. The infusion duration may be extended up to 4 hours if acute vasomotor reactions are observed. A central venous catheter is not required.
The ASADIN vial is single-dose and does not contain any preservatives. Discard unused portions of each vial properly. Do not mix ASADIN with other medications.

Safe Handling Procedures
ASADIN is a cytotoxic drug. Follow applicable special handling and disposal procedures.

2.5 Incompatibilities
In the absence of incompatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 2.4.

3. DOSAGE FORMS AND STRENGTHS
Injection: 10 mg/10 ml (1 mg/ml) arsenic trioxide clear solution in a single-dose vial.

4. CONTRAINDICATIONS
ASADIN is contraindicated in patients with hypersensitivity to arsenic.

5. WARNINGS AND PRECAUTIONS
5.1 Differentiation Syndrome
Differentiation syndrome, which may be life-threatening or fatal, has been observed in patients with acute promyelocytic leukemia (APL) treated with Arsenic Trioxide. In clinical trials, 16-23% of patients treated with Arsenic Trioxide for APL developed differentiation syndrome. Signs and symptoms include unexplained fever, dyspnea, hypoxia, acute respiratory distress, pulmonary infiltrates, pleural or pericardial effusion, weight gain, peripheral edema, hypotension, renal insufficiency, hepatopathy and multi-organ dysfunction. Differentiation syndrome has been observed with and without concomitant leukocytosis, and it has occurred as early as day 1 of induction to as late as the second month induction therapy.

When Arsenic Trioxide is used in combination with tretinoin, prophylaxis with prednisone is recommended during the induction cycle [see Dosage and Administration (2.1)].

If differentiation syndrome is suspected, temporarily withhold ASADIN and immediately initiate dexamethasone 10 mg intravenously every 12 hours and hemodynamic monitoring until resolution of signs and symptoms for a minimum of 3 days [see Dosage and Administration (2.3)].

5.2 Cardiac Conduction Abnormalities
Patients treated with Arsenic Trioxide can develop QTc prolongation, torsade de pointes, and complete atrioventricular block. In the clinical trials (APL0406 Trial) of patients with newly-diagnosed low-to-intermediate-risk APL treated with Arsenic Trioxide in combination with tretinoin, 11% experienced QTc (Framingham formula) prolongation > 450 msec for men and > 460 msec for women throughout the treatment cycles. In the clinical trial (PLRXAS01 Trial) of patients with relapsed or refractory APL treated with Arsenic Trioxide monotherapy, 40% had at least one ECG tracing with a QTc interval greater than 500 msec. A prolonged QTc was observed between 1 and 5 weeks after start of Arsenic Trioxide infusion, and it usually resolved by 8 weeks after Arsenic Trioxide infusion. There are no data on the effect of Arsenic Trioxide on the QTc interval during the infusion of the drug.

The risk of torsade de pointes is related to the extent of QTc prolongation, concomitant administration of QTc prolonging drugs, a history of torsade de pointes, pre-existing QTc interval prolongation, congestive heart failure, administration of potassium-wasting diuretics, or other conditions that result in hypokalemia or hypomagnesemia. The risk may be increased when Arsenic Trioxide is coadministered with medications that can lead to electrolyte abnormalities (such as diuretics or amphotericin B) [see Drug Interactions (7)].

Prior to initiating therapy with Arsenic Trioxide, assess the QTc interval by electrocardiogram, correct pre-existing electrolyte abnormalities, and consider discontinuing drugs known to prolong QTc interval. Do not administer Arsenic Trioxide to patients with a ventricular arrhythmia or prolonged QTc. If possible, discontinue drugs that are known to prolong the QTc interval. If it is not possible to discontinue the interacting drug, perform cardiac monitoring frequently [see Drug Interactions (7)]. During Arsenic Trioxide therapy, maintain potassium concentrations above 4 mEq/L and magnesium concentrations above 1.8 mg/dL. Monitor ECG weekly, and more frequently for clinically unstable patients.

For patients who develop a QTc greater than 450 msec, for men or greater than 460msec for women, withhold Arsenic Trioxide and any medication known to prolong the QTc interval. Correct electrolyte abnormalities. When the QTc normalizes and electrolyte abnormalities are corrected, resume Arsenic Trioxide at a reduced dose [see Dosage and Administration (2.3)].

5.3 Encephalopathy

Serious encephalopathies were reported in patients receiving Arsenic Trioxide. Monitor patients for neurological symptoms such as confusion, decreased level of consciousness, seizures, cognitive deficits, ataxia, visual symptoms and ocular motor dysfunction. Advise patients and caregivers of the need for close observation.

Wernicke's Encephalopathy

Wernicke's encephalopathy occurred in patients receiving Arsenic Trioxide. Wernicke's encephalopathy is a neurologic emergency that can be prevented and treated with thiamine. Consider testing thiamine levels in patients at risk for thiamine deficiency (e.g., chronic alcohol use, malabsorption, nutritional deficiency, concomitant use of furosemide). Administer parenteral thiamine in patients with or at risk for thiamine deficiency. Monitor patients for neurological symptoms and nutritional status while receiving Arsenic Trioxide. If Wernicke's encephalopathy is suspected, immediately interrupt Arsenic Trioxide and initiate parenteral thiamine. Monitor until symptoms resolve or improve and thiamine levels normalize.

5.4 Hepatotoxicity

In the clinical trials (APL0406 Trial), 44% of patients with newly-diagnosed low-to-intermediate-risk APL treated with Arsenic Trioxide in combination with tretinoin experienced elevated aspartate aminotransferase (AST), alkaline phosphatase, and/or serum bilirubin. These abnormalities resolved with temporary discontinuation of Arsenic Trioxide and/or tretinoin.

Long-term liver abnormalities can occur in APL patients treated with Arsenic Trioxide in combination with tretinoin. In a published series, mild liver dysfunction and hepatic steatosis were seen in 15% and 43%, respectively, of patients at a median of 7 years (range 0-14 years) after treatment with arsenic trioxide in combination with tretinoin.

During treatment with Arsenic Trioxide, monitor hepatic function tests at least twice weekly during induction and at least once weekly during consolidation. Withhold Arsenic Trioxide and/or tretinoin if elevations in AST or alkaline phosphatase occur to greater than 5 times the upper limit of normal and/or elevation in serum total bilirubin occurs to greater than 3 times the upper limit of normal and resume at reduced dose upon resolution [see Dosage and Administration (2.3)].

5.5 Carcinogenesis

The active ingredient of ASADIN, arsenic trioxide, is a human carcinogen. Monitor patients for the development of second primary malignancies.

5.6 Embryo-Fetal Toxicity

Arsenic Trioxide can cause fetal harm when

administered to a pregnant woman. Arsenic trioxide was embryolethal and teratogenic in rats when administered on gestation day 9 at a dose approximately 10 times the recommended human daily dose on a mg/m^2 basis. A related trivalent arsenic, sodium arsenite, produced teratogenicity when administered during gestation in mice at a dose approximately 5 times the projected human dose on a mg/m^2 basis and in hamsters at an intravenous dose approximately equivalent to the projected human daily dose on a mg/m^2 basis.

Advise pregnant women of the potential risk to a fetus. Advise females and males of reproductive potential to use effective contraception during treatment with Arsenic Trioxide and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Arsenic Trioxide and for 3 months after the last dose [see Use in Specific Populations (8.1, 8.3)].

5.7 Hyperleucocytosis

Treatment with Arsenic Trioxide has been associated with the development of hyperleucocytosis (≥ 10 x 10^3/µl) in some relapsed/refractory APL patients (PLRXAS01 Trial). There did not appear to be a relationship between baseline white blood cell (WBC) counts and development of hyperleucocytosis nor did there appear to be a correlation between baseline WBC count and peak WBC counts. Hyperleucocytosis was never treated with additional chemotherapy and resolved on continuation of Arsenic Trioxide. WBC counts during consolidation were not as high as during induction treatment and were < 10 x 10^3/µl, except in one patient who had a WBC count of 22 x 10^3/µl during consolidation. Twenty relapsed/refractory APL patients (50 %) experienced leucocytosis; however, in all these patients, the WBC count was declining or had normalized by the time of bone marrow remission and cytotoxic chemotherapy or leucopheresis was not required. In newly diagnosed patients with low-to-intermediate-risk APL (APL0406 Trial) leucocytosis developed during induction therapy in 35 of 74 (47 %) patients (see section 4.8). However all cases were successfully managed with hydroxyurea therapy.
In newly diagnosed and relapsed/refractory APL patients who develop sustained leucocytosis after initiation of therapy, hydroxyurea should be administered. Hydroxyurea should be continued at a given dose to keep the white blood cell count ≤ 10 x 10^3/µl and subsequently tapered.

6. ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling.

- Differentiation Syndrome [see Warnings and Precautions (5.1)]
- Cardiac Conduction Abnormalities [see Warnings and Precautions (5.2)]
- Encephalopathy [see Warnings and Precautions (5.3)]
- Hepatotoxicity [see Warnings and Precautions (5.4)]
- Carcinogenesis [see Warnings and Precautions (5.5)]

6.1 Clinical Trials Experience

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

Newly-Diagnosed Low-to-Intermediate-Risk APL

The safety of Arsenic Trioxide in combination with tretinoin was evaluated in Study APL0406, a randomized trial comparing Arsenic Trioxide plus tretinoin (n=129) versus chemotherapy plus tretinoin (n=137) in patients with newly-diagnosed APL [see Clinical Studies (14.1)]. In the Arsenic Trioxide /tretinoin group, 98% of patients completed induction therapy and 89% completed at least three consolidation cycles. In the chemotherapy/tretinoin group, 96% completed induction therapy and 87% patients completed all three courses of consolidation therapy.

Serious adverse reactions reported in 25% of the patients on the Arsenic Trioxide/tretinoin arm and 24% on the chemotherapy/tretinoin arm. The serious adverse reactions reported in ≥ 2% of patients receiving Arsenic Trioxide/tretinoin were abnormal liver tests, differentiation syndrome, dyspnea, pneumonia, and other infections.Fatal adverse reactions were reported in 1 (1%) patient on the Arsenic Trioxide/tretinoin arm and 8 (6%) patients on the chemotherapy/tretinoin arm.

Arsenic Trioxide/tretinoin was discontinued due to toxicity in 1 patient during induction and in 4 patients during the first three consolidation courses, whereas chemotherapy/tretinoin was discontinued due to toxicity in 4 patients during induction and in 6 patients during consolidation.

Selected hematologic and nonhematologic toxicities that occurred during induction or consolidation are presented in Table 4.

Table 4 **Selected Adverse Reactions of Arsenic Trioxide in Combination with Tretinoin in Patients with Newly-Diagnosed APL in Study APL0406**

Adverse Reaction	**Induction n (%)**	**Consolidation n (%)**		
		1st	**2nd**	**3rd**
Thrombocytopenia > 15 days (Grade 3-4)				
ATO/ATRA	74 (58%)	6 (5%)	6 (5%)	8 (7%)
CHT/ATRA	120 (88%)	17 (14%)	77 (63%)	26 (22%)
Neutropenia> 15 days (Grade 3-4)				
ATO/ATRA	61 (48%)	8 (7%)	7 (6%)	5 (4%)
CHT/ATRA	109 (80%)	40 (32%)	90 (73%)	28 (24%)
Hepatic toxicity (Grade 3-4)				
ATO/ATRA	51 (40%)	5 (4%)	1 (1%)	0 (0%)
CHT/ATRA	4 (3%)	1 (1%)	0 (0%)	0 (0%)
Infection and fever of unknown origin				
ATO/ATRA	30 (23%)	10 (8%)	4 (3%)	2 (2%)
CHT/ATRA	75 (55%)	8 (6%)	46 (38%)	2 (2%)
Hypertriglyceridemia				
ATO/ATRA	29 (22%)	22 (18%)	17 (14%)	16 (14%)
CHT/ATRA	29 (22%)	19 (15%)	10 (8%)	13 (11%)
Hypercholesterolemia				
ATO/ATRA	14 (10%)	19 (16%)	19 (16%)	16 (14%)
CHT/ATRA	12 (9%)	12 (10%)	12 (10%)	11 (9%)
QT prolongation				
ATO/ATRA	11 (9%)	3 (2%)	3 (2%)	2 (2%)

Adverse Reaction	Induction n (%)	Consolidation n (%)		
		1st	2nd	3rd
CHT/ATRA	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Gastrointestinal toxicity (Grade 3-4)				
ATO/ATRA	3 (2%)	0 (0%)	0 (0%)	0 (0%)
CHT/ATRA	25 (18%)	1 (1%)	6 (5%)	0 (0%)
Neurotoxicity*				
ATO/ATRA	1 (1%)	5 (4%)	6 (5%)	7 (6%)
CHT/ATRA	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cardiac function (Grade 3-4)				
ATO/ATRA	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CHT/ATRA	5 (4%)	0 (0%)	0 (0%)	0 (0%)

*Mostly cases of reversible peripheral neuropathy

ATO: Arsenic Trioxide; ATRA: Tretinoin; CHT: chemotherapy

Relapsed or Refractory APL

Safety information was available for 52 patients with relapsed or refractory APL who participated in clinical trials of Arsenic Trioxide. Forty patients in the Study PLRXAS01 received the recommended dose of 0.15 mg/kg, of whom 28 completed both induction and consolidation treatment cycles. An additional 12 patients with relapsed or refractory APL received doses generally similar to the recommended dose.

Serious adverse reactions observed in the 40 patients with refractory or relapsed APL enrolled in Study PLRXAS01 included differentiation syndrome (n=3), hyperleukocytosis (n=3), QTc interval ≥ 500 msec (n=16, 1 with torsade de pointes), atrial dysrhythmias (n=2), and hyperglycemia (n=2).

Most patients experienced some drug-related toxicity, most commonly leukocytosis, gastrointestinal (nausea, vomiting, diarrhea, and abdominal pain), fatigue, edema, hyperglycemia, dyspnea, cough, rash or itching, headaches, and dizziness. These adverse effects have not been observed to be permanent or irreversible nor do they usually require interruption of therapy.

The most common adverse reactions (> 30%) were nausea, cough, fatigue, pyrexia, headache, abdominal pain, vomiting, tachycardia, diarrhea, dyspnea, hypokalemia, leukocytosis, hyperglycemia, hypomagnesemia, insomnia, dermatitis, edema, QTc prolongation, rigors, sore throat, arthralgia, paresthesia, and pruritus.

Table 5 describes the adverse reactions in patients aged 5 to 73 years with APL who received Arsenic Trioxide at the recommended dose. Similar adverse reactions profiles were seen in the other patient populations who received Arsenic Trioxide.

Table 5 **Adverse Reactions (≥ 5%) in Patients with Relapsed or Refractory APL Who Received Arsenic Trioxide in Study PLRXAS01**

Body System Adverse reaction	Any Grade Adverse Reactions		Grade ≥3 Adverse Reactions	
	n	%	n	%
Gastrointestinal disorders				
Nausea	30	75		
Abdominal pain (lower & upper)	23	58	4	10
Vomiting	23	58		
Diarrhea	21	53		
Sore throat	14	35		
Constipation	11	28	1	3
Anorexia	9	23		
Appetite decreased	6	15		
Loose stools	4	10		
Dyspepsia	4	10		

Body System Adverse reaction	Any Grade Adverse Reactions		Grade ≥3 Adverse Reactions	
	n	%	n	%
Oral blistering	3	8		
Fecal incontinence	3	8		
Gastrointestinal hemorrhage	3	8		
Dry mouth	3	8		
Abdominal tenderness	3	8		
Diarrhea hemorrhagic	3	8		
Abdominal distension	3	8		
Respiratory				
Cough	26	65		
Dyspnea	21	53	4	10
Epistaxis	10	25		
Hypoxia	9	23	4	10
Pleural effusion	8	20	1	3
Post nasal drip	5	13		
Wheezing	5	13		
Decreased breath sounds	4	10		
Crepitations	4	10		
Rales	4	10		
Hemoptysis	3	8		
Tachypnea	3	8		
Rhonchi	3	8		
General disorders and administration site conditions				
Fatigue	25	63	2	5
Pyrexia (fever)	25	63	2	5
Edema - non-specific	16	40		
Rigors	15	38		
Chest pain	10	25	2	5
Injection site pain	8	20		
Pain - non-specific	6	15	1	3
Injection site erythema	5	13		
Weight gain	5	13		
Injection site edema	4	10		
Weakness	4	10	2	5
Hemorrhage	3	8		

Body System Adverse reaction	Any Grade Adverse Reactions		Grade ≥3 Adverse Reactions	
	n	%	n	%
Weight loss	3	8		
Drug hypersensitivity	2	5	1	3
Nervous system disorders				
Headache	24	60	1	3
Insomnia	17	43	1	3
Paresthesia	13	33	2	5
Dizziness (excluding vertigo)	9	23		
Tremor	5	13		
Convulsion	3	8	2	5
Somnolence	3	8		
Coma	2	5	2	5
Cardiac disorders				
Tachycardia	22	55		
ECG QT corrected interval prolonged > 500 msec	16	40		
Palpitations	4	10		
ECG abnormal other than QT interval prolongation	3	8		
Metabolism and nutrition disorders				
Hypokalemia	20	50	5	13
Hypomagnesemia	18	45	5	13
Hyperglycemia	18	45	5	13
ALT increased	8	20	2	5
Hyperkalemia	7	18	2	5
AST increased	5	13	1	3
Hypocalcemia	4	10		
Hypoglycemia	3	8		
Acidosis	2	5		
Hematologic disorders				
Leukocytosis	20	50	1	3
Anemia	8	20	2	5
Thrombocytopenia	7	18	5	13
Febrile neutropenia	5	13	3	8
Neutropenia	4	10	4	10

Body System Adverse reaction	Any Grade Adverse Reactions		Grade ≥3 Adverse Reactions	
	n	%	n	%
Disseminated intravascular coagulation	3	8	3	8
Lymphadenopathy	3	8		
Skin and subcutaneous tissue disorders				
Dermatitis	17	43		
Pruritus	13	33	1	3
Ecchymosis	8	20		
Dry skin	6	15		
Erythema - non-specific	5	13		
Increased sweating	5	13		
Facial edema	3	8		
Night sweats	3	8		
Petechiae	3	8		
Hyperpigmentation	3	8		
Non-specific skin lesions	3	8		
Urticaria	3	8		
Local exfoliation	2	5		
Eyelid edema	2	5		
Musculoskeletal, connective tissue, and bone disorders				
Arthralgia	13	33	3	8
Myalgia	10	25	2	5
Bone pain	9	23	4	10
Back pain	7	18	1	3
Neck pain	5	13		
Pain in limb	5	13	2	5
Psychiatric disorders				
Anxiety	12	30		
Depression	8	20		
Agitation	2	5		
Confusion	2	5		
Vascular disorders				
Hypotension	10	25	2	5
Flushing	4	10		
Hypertension	4	10		
Pallor	4	10		
Infections and infestations				
Sinusitis	8	20		
Herpes simplex	5	13		
Upper respiratory tract infection	5	13	1	3
Bacterial infection - non-specific	3	8	1	3
Herpes zoster	3	8		
Nasopharyngitis	2	5		
Oral candidiasis	2	5		
Sepsis	2	5	2	5
Reproductive system disorders				
Vaginal hemorrhage	5	13		
Intermenstrual bleeding	3	8		
Ocular disorders				
Eye irritation	4	10		
Blurred vision	4	10		
Dry eye	3	8		
Painful red eye	2	5		
Renal and urinary disorders				
Renal failure	3	8	1	3
Renal impairment	3	8		
Oliguria	2	5		
Incontinence	2	5		
Ear disorders				
Earache	3	8		
Tinnitus	2	5		

Other Clinically Relevant Adverse Reactions

Leukocytosis: Arsenic Trioxide can induce proliferation of leukemic promyelocytes resulting in a rapid increase in white blood cell count. Leukocytosis greater than 10 Gi/L developed during induction therapy in 43% patients receiving Arsenic Trioxide/tretinoin for newly-

diagnosed low-to-intermediate-risk APL and in 50% of patients receiving Arsenic Trioxide monotherapy for relapsed/refractory APL. In the relapsed/refractory setting, a relationship did not exist between baseline WBC counts and development of hyperleukocytosis nor baseline WBC counts and peak WBC counts.

6.2 Postmarketing Experience

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

Cardiac disorders: Ventricular extrasystoles in association with QT prolongation, ventricular tachycardia in association with QT prolongation, including torsade de pointes, atrioventricular block, and congestive heart failure

Ear and labyrinth disorders: Deafness

Hematologic disorders: Pancytopenia, bone marrow necrosis

Infections: Herpes zoster

Investigations: Gamma-glutamyltransferase increased

Musculoskeletal and connective tissue disorders: Bone pain, myalgia, rhabdomyolysis

Neoplasms benign, malignant and unspecified: Melanoma, pancreatic cancer, squamous cell carcinoma

Nervous system disorders: Peripheral neuropathy, paresis, seizures, confusion, encephalopathy, Wernicke's encephalopathy, posterior reversible encephalopathy syndrome

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis

7. DRUG INTERACTIONS

Drugs That Can Prolong the QT/QTc Interval

Concomitant use of these drugs and Arsenic Trioxide may increase the risk of serious QT/QTc interval prolongation [see Warnings and Precautions (5.1)]. Discontinue or replace with an alternative drug that does not prolong the QT/QTc interval while patient is using Arsenic Trioxide. Monitor ECGs more frequently in patients when it is not feasible to avoid concomitant use.

Drugs That Can Lead to Electrolyte Abnormalities

Electrolyte abnormalities increase the risk of serious QT/QTc interval prolongation [see Warnings and Precautions (5.1)]. Avoid concomitant administration of drugs that can lead to electrolyte abnormalities. Monitor electrolytes more frequently in patients who must receive concomitant use of these drugs and Arsenic Trioxide.

Drugs That Can Lead to Hepatotoxicity

Concomitant use of these drugs and Arsenic Trioxide, particularly when given in combination with tretinoin, may increase the risk of serious hepatotoxicity [see Warnings and Precautions (5.4)]. Discontinue or replace with an alternative drug that does not cause hepatotoxicity while the patient is using Arsenic Trioxide. Monitor liver function tests more frequently in patients when it is not feasible to avoid concomitant use.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on the mechanism of action [see Clinical Pharmacology (12.1)] and findings in animal studies, Arsenic Trioxide can cause fetal harm when administered to a pregnant woman. Arsenic Trioxide was embryolethal and teratogenic in rats when administered on gestation day 9 at a dose approximately 10 times the recommended human daily dose on a mg/m^2 basis (see *Data*). A related trivalent arsenic, sodium arsenite, produced teratogenicity when administered during gestation in mice at a dose approximately 5 times the projected human dose on a mg/m^2 basis and in hamsters at an intravenous dose approximately equivalent to the projected human daily dose on a mg/m^2 basis. There are no studies with the use of Arsenic Trioxide in pregnant women, and limited published data on Arsenic Trioxide use during pregnancy are insufficient to inform a drug associated

risk of major birth defects and miscarriage. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

Data

Human Data

One patient was reported to deliver a live infant with no reported congenital anomalies after receiving Arsenic Trioxide during the first five months of pregnancy. A second patient became pregnant three months after discontinuing Arsenic Trioxide and was reported to have a normal pregnancy outcome. A third patient was a pregnant healthcare provider who experienced dermal contact with liquid arsenic trioxide and had a normal pregnancy outcome after treatment and monitoring. A fourth patient who became pregnant while receiving Arsenic Trioxide had a miscarriage.

Animal Data

Studies in pregnant mice, rats, hamsters, and primates have shown that inorganic arsenicals cross the placental barrier when given orally or by injection. An increase in resorptions, neural-tube defects, anophthalmia and microphthalmia were observed in rats administered 10 mg/kg of Arsenic Trioxide on gestation day 9 (approximately 10 times the recommended human daily dose on a mg/m^2 basis). Similar findings occurred in mice administered a 10 mg/kg dose of a related trivalent arsenic, sodium arsenite (approximately 5 times the projected human dose on a mg/m^2 basis), on gestation days 6, 7, 8, or 9. Intravenous injection of 2 mg/kg sodium arsenite (approximately equivalent to the projected human daily dose on a mg/m^2 basis) on gestation day 7 (the lowest dose tested) resulted in neural-tube defects in hamsters.

8.2 Lactation

Risk Summary

Arsenic Trioxide is excreted in human milk. There are no data on the effects of Arsenic Trioxide on the breastfed child or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with Arsenic Trioxide and for 2 weeks after the final dose.

8.3 Females and Males of Reproductive Potential

Arsenic Trioxide can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

Pregnancy Testing

Conduct pregnancy testing in females of reproductive potential prior to initiation of treatment with Arsenic Trioxide.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with Arsenic Trioxide and for 6 months after the final dose.

Males

Advise males with female partners of reproductive potential to use effective contraception during and after treatment with Arsenic Trioxide and for three months after the final dose.

Infertility

Males

Based on testicular toxicities including decreased testicular weight and impaired spermatogenesis observed in animal studies, Arsenic Trioxide may impair fertility in males of reproductive potential [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

The safety and efficacy of Arsenic Trioxide in children aged up to 17 years has not been established. Currently available data for children aged 5 to 16 years are described in section 13.2 but no recommendation on a

posology can be made. No data are available for children under 5 years.

8.5 Geriatric Use

There is limited clinical data on the use of Arsenic Trioxide in the elderly population. Caution is needed in these patients.

8.6 Renal Impairment

Exposure of Arsenic Trioxide may be higher in patients with severe renal impairment [see Clinical Pharmacology (12.3)]. Monitor patients with severe renal impairment (creatinine clearance [CLcr] less than 30 mL/min) frequently for toxicity; a dose reduction may be warranted.

The use of Arsenic Trioxide in patients on dialysis has not been studied.

8.7 Hepatic Impairment

Since limited data are available across all hepatic impairment groups, caution is advised in the use of Arsenic Trioxide in patients with hepatic impairment [see Clinical Pharmacology (12.3)].
Monitor patients with severe hepatic impairment (Child-Pugh Class C) frequently for toxicity.

9. OVERDOSAGE

Manifestations

Manifestations of Arsenic Trioxide overdosage include convulsions, muscle weakness, and confusion.

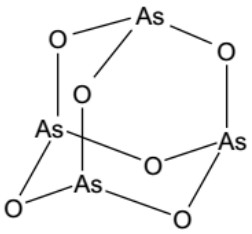
Management

For symptoms of Arsenic Trioxide overdosage immediately discontinue Arsenic Trioxide and consider chelation therapy.

A conventional protocol for acute arsenic intoxication includes dimercaprol administered at a dose of 3 mg/kg intramuscularly every 4 hours until immediate life-threatening toxicity has subsided. Thereafter, penicillamine at a dose of 250 mg orally, up to a maximum frequency of four times per day (≤ 1 g per day), may be given.

10. DESCRIPTION

ASADIN is a sterile injectable solution of Arsenic Trioxide. The molecular formula of the drug substance in the solid state is As_2O_3, with a molecular weight of 197.8 and has the following structural formula:



ASADIN is available in 10 mL, single-dose vials (Type 1 clear glass vials, and closure with chlorobutyl rubber stoppers and flip off white aluminum seals) containing 10 mg of Arsenic Trioxide.
ASADIN is formulated as a sterile, nonpyrogenic, clear solution of Arsenic Trioxide in water for injection using sodium hydroxide and dilute hydrochloric acid to adjust to pH 8. ASADIN is preservative-free. Arsenic Trioxide, the active ingredient, is present at a concentration of 1 mg/mL. Inactive ingredients and their respective approximate concentrations are sodium hydroxide (1.2 mg/mL), and sodium hydroxide and hydrochloric acid for pH adjustment to pH 8.

11. CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

The mechanism of action of Arsenic Trioxide is not completely understood. Arsenic Trioxide causes morphological changes and DNA fragmentation characteristic of apoptosis in NB4 human promyelocytic leukemia cells in vitro. Arsenic Trioxide also causes damage or degradation of the fusion protein promyelocytic leukemia (PML)-retinoic acid receptor (RAR)-alpha.

11.2 Pharmacodynamics

Cardiac Electrophysiology

In a single-arm trial of Arsenic Trioxide (0.15 mg/kg

daily), 16 of 40 patients (40%) had a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after Arsenic Trioxide infusion, and then returned towards baseline by the end of 8 weeks after Arsenic Trioxide infusion.

11.3 Pharmacokinetics

The inorganic, lyophilized form of Arsenic Trioxide, when placed into solution, immediately forms the hydrolysis product arsenious acid (As^{III}). As^{III} is the pharmacologically active species of Arsenic Trioxide. Monomethylarsonic acid (MMA^{V}), and dimethylarsinic acid (DMA^{V}) are the main pentavalent metabolites formed during metabolism, in addition to arsenic acid (As^{V}) a product of As^{III} oxidation.

The pharmacokinetics of arsenical species ([As^{III}], [As^{V}], [MMA^{V}], [DMA^{V}]) were determined in 6 APL patients following once-daily doses of 0.15 mg/kg for 5 days per week. Over the total single-dose range of 7 to 32 mg (administered as 0.15 mg/kg), systemic exposure (AUC) appears to be linear.

Peak plasma concentrations of arsenious acid (As^{III}), the primary active arsenical species were reached at the end of infusion (2 hours). Plasma concentration of As^{III} declined in a biphasic manner with a mean elimination half-life of 10 to 14 hours and is characterized by an initial rapid distribution phase followed by a slower terminal elimination phase. The daily exposure to As^{III} (mean AUC_{0-24}) was 194 ng·hr/mL (n=5) on Day 1 of Cycle 1 and 332 ng·hr/mL (n=6) on Day 25 of Cycle 1, which represents an approximate 2-fold accumulation.

The primary pentavalent metabolites, MMA^{V} and DMA^{V}, are slow to appear in plasma (approximately 10-24 hours after first administration of Arsenic Trioxide), but, due to their longer half-life, accumulate more upon multiple dosing than does As^{III}. The mean estimated terminal elimination half-lives of the metabolites MMA^{V} and DMA^{V} are 32 hours and 72 hours, respectively. Approximate accumulation ranged from 1.4- to 8-fold following multiple dosing as compared to single-dose administration. As^{V} is present in plasma only at relatively low levels.

Distribution

The volume of distribution (V_{ss}) for As^{III} is large (mean 562 L, N=10) indicating that As^{III} is widely distributed throughout body tissues. V_{ss} is also dependent on body weight and increases as body weight increases.

Elimination

Metabolism

Much of the As^{III} is distributed to the tissues where it is methylated to the less cytotoxic metabolites, monomethylarsonic acid (MMA^{V}) and dimethylarsinic acid (DMA^{V}) by methyltransferases primarily in the liver. The metabolism of Arsenic Trioxide also involves oxidation of As^{III} to As^{V}, which may occur in numerous tissues via enzymatic or nonenzymatic processes. As^{V} is present in plasma only at relatively low levels following administration of Arsenic Trioxide.

Excretion

Approximately 15% of the administered Arsenic Trioxide dose is excreted in the urine as unchanged As^{III}. The methylated metabolites of As^{III} (MMA^{V}, DMA^{V}) are primarily excreted in the urine. The total clearance of As^{III} is 49 L/h and the renal clearance is 9 L/h. Clearance is not dependent on body weight or dose administered over the range of 7-32 mg.

Specific Populations

Patients with Renal Impairment

The effect of renal impairment on the pharmacokinetics of As^{III}, As^{V}, and the pentavalent metabolites MMA^{V} and DMA^{V} was evaluated in 20 patients with advanced malignancies. Patients were classified as having normal renal function (creatinine clearance [CrCl] > 80 mL/min, n=6), mild renal impairment (CrCl 50-80 mL/min, n=5), moderate renal impairment (CrCl 30-49 mL/min, n=6), or severe renal impairment (CrCl < 30 mL/min, n=3). Following twice-weekly administration of 0.15 mg/kg

over a 2-hour infusion, the mean $AUC_{0-\infty}$ for As^{III} was comparable among the normal, mild and moderate renal impairment groups. However, in the severe renal impairment group, the mean $AUC_{0-\infty}$ for As^{III} was approximately 48% higher than that in the normal group.

Systemic exposure to MMA^{V} and DMA^{V} tended to be larger in patients with renal impairment; however, the clinical consequences of this increased exposure are not known. As^{V} plasma levels were generally below the limit of assay quantitation in patients with impaired renal function [see Use in Specific Populations (8.6)]. The use of Arsenic Trioxide in patients on dialysis has not been studied.

Patients with Hepatic Impairment

The effect of pharmacokinetics of As^{III}, As^{V}, and the pentavalent metabolites MMA^{V} and DMA^{V} was evaluated following administration of 0.25-0.50 mg/kg of Arsenic Trioxide in patients with hepatocellular carcinoma. Patients were classified as having normal hepatic function (n=4), mild hepatic impairment (Child-Pugh class A, n=12), moderate hepatic impairment (Child-Pugh class B, n=3), or severe hepatic impairment (Child-Pugh class C, n=1). No clear trend toward an increase in systemic exposure to As^{III}, $As^{V,}$ MMA^{V} or DMA^{V} was observed with decreasing level of hepatic function as assessed by dose-normalized (per mg dose) AUC in the mild and moderate hepatic impairment groups. However, the one patient with severe hepatic impairment had mean dose-normalized AUC_{0-24} and C_{max} values 40% and 70% higher, respectively, than those patients with normal hepatic function. The mean dose-normalized trough plasma levels for both MMA^{V} and DMA^{V} in this severely hepatically impaired patient were 2.2-fold and 4.7-fold higher, respectively, than those in the patients with normal hepatic function [see Use in Specific Populations (8.7)].

Pediatric Patients

Following IV administration of 0.15 mg/kg/day of Arsenic Trioxide in 10 APL patients (median age = 13.5 years, range 4-20 years), the daily exposure to As^{III} (mean AUC_{0-24h}) was 317 ng·hr/mL on Day 1 of Cycle 1 [see Use in Specific Populations (8.4)].

Drug Interaction Studies

No formal assessments of pharmacokinetic drug-drug interactions between Arsenic Trioxide and other drugs have been conducted. The methyltransferases responsible for metabolizing Arsenic Trioxide are not members of the cytochrome P450 family of isoenzymes. In vitro incubation of Arsenic Trioxide with human liver microsomes showed no inhibitory activity on substrates of the major cytochrome P450 (CYP) enzymes such as 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5, and 4A9/11. The pharmacokinetics of drugs that are substrates for these CYP enzymes are not expected to be affected by concomitant treatment with Arsenic Trioxide.

12. NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with Arsenic Trioxide [see Warnings and Precautions (5.6)].

Arsenic Trioxide and trivalent arsenite salts have not been demonstrated to be mutagenic to bacteria, yeast, or mammalian cells. Arsenite salts are clastogenic in vitro (human fibroblast, human lymphocytes, Chinese hamster ovary cells, Chinese hamster V79 lung cells). Trivalent arsenic was genotoxic in the chromosome aberrations assay and micronucleus bone marrow assay in mice.

The effect of arsenic on fertility has not been adequately studied in humans. Decreased testicular weight and impaired spermatogenesis have been reported in animal studies. Male Wistar rat pups were administered 1.5 mg/kg sodium arsenite solution via the intraperitoneal route from postnatal days 1 to 14 and testes were collected for evaluation on postnatal days 15, 21, and 50. Results of this study revealed an altered morphology

of the seminiferous tubules along with degeneration of spermatogenic cells, increased number of sperm with abnormal morphology, and decreased sperm counts. In beagle dogs administered intravenous Arsenic Trioxide for 90 days, reduced inner cell layers within seminiferous tubules and significantly decreased numbers of spermatocytes, spermatozoa, and sperm cells were observed at doses of 1 mg/kg/day and higher. The 1 mg/kg/day dose is approximately 3 times the recommended human daily dose on a mg/m^2 basis.

13. CLINICAL STUDIES

13.1 Newly-Diagnosed Low-to-Intermediate-Risk APL

Arsenic Trioxide in combination with tretinoin was investigated in Study APL0406 (NCT00482833), a multicenter, randomized, open-label trial in patients with newly-diagnosed low-to-intermediate-risk APL (white blood cell count at diagnosis ≤10 Gi/L). The patients were randomized 1:1 to receive Arsenic Trioxide /tretinoin for induction and consolidation or chemotherapy/tretinoin for induction, consolidation, and maintenance.

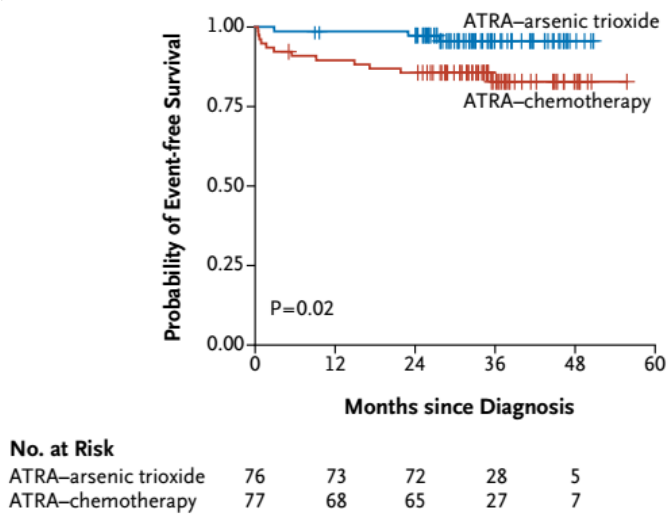
Patients in the Arsenic Trioxide/tretinoin group received induction treatment with Arsenic Trioxide 0.15 mg/kg intravenously once daily in combination with tretinoin 22.5 mg/m^2 (rounded to the nearest 10 mg increment) orally twice daily until hematologic complete remission (CR) or for a maximum of 60 days. Patients in this group who achieved a CR during induction received four 8-week cycles of consolidation treatment with Arsenic Trioxide 0.15 mg/kg intravenously once daily for 5 days every week during weeks 1-4 of the 8-week cycle, in combination with tretinoin 22.5 mg/m^2 (rounded to the nearest 10 mg increment) orally twice daily during weeks 1-2 and 5-6 of the 8-week cycle. Tretinoin was omitted during weeks 5-6 of the last cycle.

Patients in the chemotherapy/tretinoin group received idarubicin 12 mg/m^2 intravenously once daily on days 2, 4, 6, and 8 in combination with tretinoin 22.5 mg/m^2 (rounded to the nearest 10 mg increment) orally twice daily, starting on day 1, until hematologic CR or for a maximum of 60 days. Patients in this group who achieved a CR during induction received consolidation and maintenance treatment with tretinoin in combination with chemotherapy.

The trial enrolled 162 patients with a morphologic diagnosis of APL. The median age of patients was 45 years in the Arsenic Trioxide/tretinoin arm and 47 years in the chemotherapy/tretinoin arm, and 52% and 46% were male in the Arsenic Trioxide tretinoin and chemotherapy/tretinoin arms, respectively. Baseline characteristics were balanced between treatment arms, including median WBC count, platelet count, PML-RARA isoform, and FLT3-ITD status.

Efficacy was based on event-free survival (EFS) rate at 2 years. EFS was defined as the time from randomization to the occurrence of treatment failure, defined as no achievement of CR or CRi after induction therapy, no achievement of molecular remission after 3 consolidation courses, molecular relapse, hematologic relapse, or death. The primary analysis of EFS was based on the difference between the two treatment arms in patients achieving EFS at 2 years. With a median follow-up of 34.4 months, the 2 year EFS rate of the modified ITT (mITT) population (patients who received at least one dose of the assigned treatment) was 94% in the Arsenic Trioxide/tretinoin arm (n=77) versus 82% in the chemotherapy/tretinoin arm (n=79), a treatment difference of 11% (95% CI: 1, 22; p-value 0.048). Overall survival (OS) for the mITT population was 99% (95% CI: 93, 100) in the Arsenic Trioxide/tretinoin arm versus 91% (95% CI: 86, 97) in the chemotherapy/tretinoin arm. The difference in 2-year OS rate between the arms was 8% (95% CI: 0, 16).

Figure 1: Event-Free Survival for Newly-Diagnosed APL



No. at Risk					
ATRA–arsenic trioxide	76	73	72	28	5
ATRA–chemotherapy	77	68	65	27	7

The number of patients in the plot is based on the mITT population.

13.2 Relapsed or Refractory APL

Arsenic Trioxide was investigated in Study PLRXAS01, an open-label, single-arm trial in 40 patients with relapsed or refractory APL who were previously treated with an anthracycline and a retinoid regimen. Patients received Arsenic Trioxide 0.15 mg/kg/day intravenously over 1 to 2 hours until the bone marrow was cleared of leukemic cells or up to a maximum of 60 days. The CR (absence of visible leukemic cells in bone marrow and peripheral recovery of platelets and white blood cells with a confirmatory bone marrow ≥ 30 days later) rate in this population of previously treated patients was 28 of 40 (70%). Among the 22 patients who had relapsed less than one year after treatment with tretinoin, there were 18 complete responders (82%). Of the 18 patients receiving Arsenic Trioxide ≥ one year from tretinoin treatment, there were 10 complete responders (55%). The median time to bone marrow remission was 44 days and to onset of CR was 53 days. Three of 5 children, 5 years or older, achieved CR. No children less than 5 years old were treated.

Three to six weeks following bone marrow remission, 31 patients received consolidation therapy with Arsenic Trioxide, at the same dose, for 25 additional days over a period up to 5 weeks. In follow-up treatment, 18 patients received further Arsenic trioxide as a maintenance course. Fifteen patients had bone marrow transplants. At last follow-up, 27 of 40 patients were alive with a median follow-up time of 484 days (range 280 to 755) and 23 of 40 patients remained in complete response with a median follow-up time of 483 days (range 280 to 755).

Cytogenetic conversion to no detection of the APL chromosome rearrangement was observed in 24 of 28 (86%) patients who met the response criteria defined above, in 5 of 5 (100%) patients who met some, but not all, of the response criteria, and 3 of 7 (43%) of patients who did not respond. RT-PCR conversions to no detection of the APL gene rearrangement were demonstrated in 22 of 28 (79%) of patients who met the response criteria, in 3 of 5 (60%) of patients who met some, but not all, of the response criteria, and in 2 of 7 (29%) of patients who did not respond.

Responses were seen across all age groups tested, ranging from 6 to 72 years. The ability to achieve a CR was similar for both genders. There were insufficient patients of Black, Hispanic, or Asian derivation to estimate relative response rates in these groups, but responses were seen in members of each group.

14. REFERENCES

1. Teva, TRISENOX USFDA package insert.
2. TEVA, Trisenox EPAR Product Information.

15. HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ASADIN (arsenic trioxide) injection is supplied as a sterile, clear, colorless solution in 10 mL glass, single-dose vials (Type I clear glass vials, and closure with chlorobutyl rubber stoppers and flip off white aluminium seals).

Each 10 ml ASADIN contains 10 mg of Arsenic Trioxide.
10ml per vial.
1 vial per box.

Storage and Handling

Please store below 30℃ and protect from light.

After dilution, ASADIN is chemically and physically stable when stored for 24 hours at room temperature or 48 hours when refrigerated at 2-8℃.

ASADIN is a cytotoxic drug. Follow applicable special handling and disposal procedures.

Expiration

Please see the label and carton.

PRODUCT OWNER

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PLANT ADDRESS

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DATE OF REVISION

2022/10