HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ARSENIC TRIOXIDE injection, for intravenous use
Initial U.S. Approval: 2000

WARNING: DIFFERENTIATION SYNDROME AND CARDIAC CONDUCTION ABNORMALITIES
See full prescribing information for complete boxed warning.

- **Patients treated with Arsenic Trioxide Injection may develop differentiation syndrome, which can be fatal. If symptoms occur, initiate high-dose steroids immediately and monitor hemodynamics. (5.1)**
- **Arsenic Trioxide Injection can cause QT interval prolongation and ventricular arrhythmia, which can be fatal. Before administering Arsenic Trioxide Injection, assess the QT interval, correct electrolyte abnormalities, and consider discontinuing drugs known to prolong QT interval. Do not administer Arsenic Trioxide Injection to patients with ventricular arrhythmia or prolonged QTcF. (2.3, 5.2)**

RECENT MAJOR CHANGES

Dosage and Administration (2.1)	01/2018
Warnings and Precautions (5.1, 5.2)	01/2018

INDICATIONS AND USAGE

Arsenic Trioxide Injection is an arsenical indicated:

- For induction of remission and consolidation in patients with APL who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression. (1.2)

DOSAGE AND ADMINISTRATION

Relapsed or refractory APL:

- *Induction:* 0.15 mg/kg intravenously daily until bone marrow remission. Do not exceed 60 doses for total induction. (2.1)
- *Consolidation:* 0.15 mg/kg intravenously daily for 25 doses over a period up to 5 weeks. (2.1)

DOSAGE FORMS AND STRENGTHS

Injection: 10 mg arsenic trioxide in 10 mL clear solution in a single-dose vial. (3)

CONTRAINDICATIONS

Hypersensitivity to arsenic. (4)

WARNINGS AND PRECAUTIONS

- Hepatotoxicity: Monitor hepatic function tests at least twice weekly during arsenic trioxide injection therapy. (5.3)
- Carcinogenesis: Arsenic trioxide is a human carcinogen. Monitor patients for the development of second primary malignancies. (5.4)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.5, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions (greater than 30%) were leukocytosis, neutropenia, thrombocytopenia, nausea, vomiting, diarrhea, abdominal pain, hepatic toxicity, fever, rigors, fatigue, insomnia, tachycardia, QTc prolongation, edema, hyperglycemia, hypokalemia, hypomagnesemia, dyspnea, cough, rash or itching, sore throat, arthralgia, headaches, paresthesia and dizziness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Lactation: Advise women not to breastfeed. (8.2)
- Renal Impairment: Monitor patients with severe renal impairment (creatinine clearance less than 30 mL/min) for toxicity when treated with Arsenic Trioxide Injection; dose reduction may be warranted. (8.6)
- Hepatic Impairment: Monitor patients with severe hepatic impairment (Child-Pugh Class C) for toxicity when treated with Arsenic Trioxide Injection (8.7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 7/2018

FRESENIUS KABI

451442A/Issued: July 2018

Arsenic Trioxide
Injection

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: DIFFERENTIATION SYNDROME AND CARDIAC CONDUCTION ABNORMALITIES

Differentiation Syndrome: Patients with acute promyelocytic leukemia (APL) treated with Arsenic Trioxide Injection have experienced symptoms of differentiation syndrome, which can be fatal if not treated. Symptoms may include fever, dyspnea, acute respiratory distress, pulmonary infiltrates, pleural or pericardial effusions, weight gain or peripheral edema, hypotension, and renal, hepatic, or multi-organ dysfunction, in the presence or absence of leukocytosis. If differentiation syndrome is suspected, immediately initiate high-dose corticosteroid therapy and hemodynamic monitoring until resolution of signs and symptoms. Temporary discontinuation of Arsenic Trioxide Injection may be required *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

WARNING: DIFFERENTIATION SYNDROME AND CARDIAC CONDUCTION ABNORMALITIES (continued)

Cardiac Conduction Abnormalities: Arsenic trioxide can cause QTc interval prolongation, complete atrioventricular block, and a torsade de pointes-type ventricular arrhythmia, which can be fatal. Before initiating therapy, assess the QTc interval, correct pre-existing electrolyte abnormalities, and consider discontinuing drugs known to prolong QTc interval. Do not administer Arsenic Trioxide Injection to patients with ventricular arrhythmia or prolonged QTcF *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

1.2 Relapsed or Refractory APL

Arsenic Trioxide Injection is indicated for induction of remission and consolidation in patients with APL who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Relapsed or Refractory APL
A treatment course including Arsenic Trioxide Injection monotherapy 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 dose of Arsenic Trioxide Injection is 0.15 mg/kg intravenously daily until bone marrow remission or up to a maximum of 60 days.
- For the consolidation cycle, the recommended dose of Arsenic Trioxide Injection is 0.15 mg/kg intravenously daily for 25 doses over a period of up to 5 weeks. Begin consolidation 3 to 6 weeks after completion of induction therapy.

2.2 Dose Modifications for Toxicities

During induction therapy, monitor coagulation studies, blood counts, and chemistries at least 2-3 times per week through recovery. During consolidation, monitor at least weekly. Management of some adverse reactions may require dose interruption, dose reduction, or permanent discontinuation of Arsenic Trioxide Injection *[see Warnings and Precautions (5) and Adverse Reactions (6)]*. Table 2 shows the dose modifications for toxicity due to Arsenic Trioxide Injection when used alone.

Table 2: Dose Adjustments for Adverse Reactions

Adverse Reaction(s)	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	• Temporarily withhold Arsenic Trioxide Injection. • Treat with 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 Arsenic Trioxide Injection by 50%. • Increase the dose of Arsenic Trioxide Injection to the recommended dosage after 7 days in the absence of recurrence of symptoms of differentiation syndrome. • If symptoms re-appear, decrease Arsenic Trioxide Injection to the previous dose.
QTc Prolongation greater than 450 msec for men or greater than 460 msec for women:	• Withhold treatment with Arsenic Trioxide Injection and any medication known to prolong the QTc interval. • Replete electrolytes. • After the QTc normalizes, resume treatment with Arsenic Trioxide Injection at a 50% reduced dose (0.075 mg/kg once daily) for 7 days. • If the 50% reduced dose is tolerated for 7 days (in the absence of QTc prolongation), increase the dose of Arsenic Trioxide Injection to 0.11 mg/kg once daily for 7 days. • The dose of Arsenic Trioxide Injection can be increased to 0.15 mg/kg in the absence of QTc prolongation during that 14-day dose-escalation period.
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	• Withhold treatment with Arsenic Trioxide Injection. • 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 back to the recommended dosage after 7 days on the reduced dose in the absence of worsening of hepatotoxicity. • Discontinue the withheld drug permanently if hepatotoxicity recurs.
Other severe or life-threatening (grade 3-4) nonhematologic reactions	• Temporarily withhold Arsenic Trioxide Injection. • When the adverse reaction resolves to no more than mild (grade 1), resume Arsenic Trioxide Injection reduced by 2 dose levels (see Table 3 below).
Moderate (grade 2) nonhematologic reactions	• Reduce the dose of Arsenic Trioxide Injection by 1 dose level (see Table 3 below).
Leukocytosis (WBC count greater than 10 Gi/L)	• Administer hydroxyurea. • 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	• Consider reducing the dose of Arsenic Trioxide Injection 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 Arsenic Trioxide Injection at 1 dose level lower (see Table 3 below).

Table 3: Dose Reduction Levels for Hematologic and Nonhematologic Toxicities

Dose Level	Arsenic Trioxide Injection mg/kg intravenously once daily
Starting level	0.15
-1	0.11
-2	0.10
-3	0.075

2.3 Instructions for Preparation and Intravenous Administration

Reconstitution
Dilute Arsenic Trioxide Injection with 100 to 250 mL 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP, using proper aseptic technique, immediately after withdrawal from the vial. Do not save any unused portions for later administration.
After dilution, Arsenic Trioxide Injection is chemically and physically stable when stored for 24 hours at room temperature and 48 hours when refrigerated.
Administration
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
Administer Arsenic Trioxide Injection intravenously 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 Arsenic Trioxide Injection vial is single-dose and does not contain any preservatives. Unused portions of each vial should be discarded properly. Do not mix Arsenic Trioxide Injection with other medications.
Safe Handling Procedures
Arsenic Trioxide Injection is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

3 DOSAGE FORMS AND STRENGTHS

Injection: 10 mg arsenic trioxide in 10 mL clear solution in a single-dose vial

4 CONTRAINDICATIONS

Arsenic Trioxide Injection is contraindicated in patients who are hypersensitive 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 Injection. In clinical trials, 23% of patients treated with Arsenic Trioxide Injection for APL developed differentiation syndrome. Symptoms include unexplained fever, dyspnea, hypoxia, 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 hyperleukocytosis, and it has occurred as early as day 1 of induction to as late as the second month induction therapy.

At the first signs of differentiation syndrome, interrupt treatment with Arsenic Trioxide Injection and administer dexamethasone 10 mg intravenously twice daily. Continue high-dose steroids until signs and symptoms have abated for at least 3 days *[see Dosage and Administration (2.2)]*.

5.2 Cardiac Conduction Abnormalities

Patients treated with Arsenic Trioxide Injection can develop QTc prolongation, torsade de pointes, and complete heart block. In the clinical trial of patients with relapsed or refractory APL treated with Arsenic Trioxide Injection 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 Injection infusion, and it usually resolved by 8 weeks after Arsenic Trioxide Injection infusion. There are no data on the effect of Arsenic Trioxide Injection 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 Injection 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 Injection, 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 Injection to patients with 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 Injection 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 500 msec, immediately withhold treatment with Arsenic Trioxide Injection and any medication known to prolong the QTc interval. Correct electrolyte abnormalities. When the QTc normalizes, resume Arsenic Trioxide Injection at a reduced dose *[see Dosage and Administration (2.2)]*.

5.3 Hepatotoxicity

During treatment with Arsenic Trioxide Injection, monitor liver chemistries at least 2-3 times per week through recovery from toxicities. Withhold treatment with Arsenic Trioxide Injection if elevations in aspartate aminotransferase (AST), alkaline phosphatase, and/or serum bilirubin occur to greater than 5 times the upper limit of normal *[see Dosage and Administration (2.2)]*.
Long-term liver abnormalities can occur in APL patients treated with Arsenic Trioxide Injection.

5.4 Carcinogenesis

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

5.5 Embryo-Fetal Toxicity

Arsenic Trioxide Injection 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/m² 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/m² basis and in hamsters at an intravenous dose approximately equivalent to the projected human daily dose on a mg/m² basis. Advise pregnant women of the potential risk to a fetus. Advise females and males of reproductive potential to use effective contraception during and after treatment with Arsenic Trioxide Injection *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following serious 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)]*
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*
- Carcinogenesis *[see Warnings and Precautions (5.4)]*
- Embryo-Fetal Toxicity *[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.

Relapsed or Refractory APL
Safety information was available for 52 patients with relapsed or refractory APL who participated in clinical trials of Arsenic Trioxide Injection. Forty patients in the Phase 2 study 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. 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.

SAEs, Grade ≥3 according to version 2 of the NCI Common Toxicity Criteria, were common. Those SAEs attributed to Arsenic Trioxide Injection in the Phase 2 study of 40 patients with refractory or relapsed APL included APL differentiation syndrome (n=3), hyperleukocytosis (n=3), QTc interval ≥ 500 msec (n=16, 1 with torsade de pointes), atrial dysrhythmias (n=2), and hypertensia (n=2).

Table 5 describes the adverse reactions that were observed in ≥ 5% patients, between the ages of 5-73 years, treated for APL with Arsenic Trioxide Injection at the recommended dose. Similar adverse reactions profiles were seen in the other patient populations who received Arsenic Trioxide Injection.

Table 5: Adverse Reactions (Any Grade) Occurring in ≥ 5% of Patients Treated with Arsenic Trioxide Injection Monotherapy for Relapsed or Refractory APL

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		
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		
Weight loss	3	8		
Drug hypersensitivity	2	5	1	3

Table 5: Adverse Reactions (Any Grade) Occurring in ≥ 5% of Patients Treated with Arsenic Trioxide Injection Monotherapy for Relapsed or Refractory APL (cont'd.)

Body System Adverse reaction	Any Grade Adverse Reactions		Grade ≥ 3 Adverse Reactions	
	n	%	n	%
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
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

Table 5: Adverse Reactions (Any Grade) Occurring in ≥ 5% of Patients Treated with Arsenic Trioxide Injection Monotherapy for Relapsed or Refractory APL (cont'd.)

Body System Adverse reaction	Any Grade Adverse Reactions		Grade ≥ 3 Adverse Reactions	
	n	%	n	%
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		

Leukocytosis: Leukocytosis greater than 10 Gi/L developed during induction therapy in 50% of patients receiving Arsenic Trioxide Injection monotherapy for relapsed/refractory APL. A relationship did not exist between baseline WBC counts and development of hyperleukocytosis nor baseline WBC counts and peak WBC counts. Hyperleukocytosis due to Arsenic Trioxide Injection may warrant treatment with hydroxyurea *[see Dosage and Administration (2.2)]*.

6.2 Postmarketing Experience

The following reactions have been reported from clinical trials and/or worldwide postmarketing surveillance. Because they are reported from a population of unknown size, precise estimates of frequency cannot be made.

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

Nervous system disorders: Peripheral neuropathy, paresis, seizures, confusion

Hematologic disorders: Pancytopenia, bone marrow necrosis

Infections and infestations: Herpes zoster

Investigations: Gamma-glutamyltransferase increased

Musculoskeletal and connective tissue disorders: Bone pain, myalgia, rhabdomyolysis **Respiratory, thoracic, and mediastinal disorders:** Differentiation syndrome, like retinoic acid syndrome, has been reported with the use of Arsenic Trioxide Injection for the treatment of malignancies other than APL *[see Boxed Warning]*.

Ear and labyrinth disorders: Deafness

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

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 Injection may increase the risk of serious QT/QTc interval prolongation. Discontinue or replace with an alternative drug that does not prolong the QT/QTc interval while patient is using Arsenic Trioxide Injection. 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. 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 Injection.

Drugs That Can Lead to Hepatotoxicity
Use of these drugs and Arsenic Trioxide Injection may increase the risk of serious hepatotoxicity. Discontinue or replace with an alternative drug that does not cause hepatotoxicity while the patient is using Arsenic Trioxide Injection. 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 Injection 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/m² 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/m² basis and in hamsters at an intravenous dose approximately equivalent to the projected human daily dose on a mg/m² basis. There are no studies with the use of Arsenic Trioxide Injection 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. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

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 arsenic crosses 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 is no information 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 from Arsenic Trioxide Injection, discontinue breastfeeding during treatment with Arsenic Trioxide Injection and for two weeks after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Arsenic Trioxide Injection can cause fetal harm when administered to a pregnant woman. Conduct pregnancy testing in females of reproductive potential prior to initiation of treatment with Arsenic Trioxide Injection *[see Use in Specific Populations (8.1)]*.

Contraception

Females

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

Males

Advise males with female sexual partners of reproductive potential to use effective contraception during and after treatment with Arsenic Trioxide Injection 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 Injection may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and efficacy of Arsenic Trioxide Injection as a single agent for treatment of pediatric patients with relapsed or refractory APL is supported by the pivotal phase 2 study in 40 patients with relapsed or refractory APL. Five patients below the age of 18 years (age range: 5 to 16 years) were treated with Arsenic Trioxide Injection at the recommended dose of 0.15 mg/kg/day. A literature review included an additional 17 patients treated with arsenic trioxide for relapsed or refractory APL, with ages ranging from 4 to 21 years. No differences in efficacy and safety were observed by age.

8.5 Geriatric Use

The safety and efficacy of Arsenic Trioxide Injection as a single agent in older patients with relapsed or refractory APL is supported by the pivotal phase 2 study in 40 patients with relapsed or refractory APL. Six patients age 65 and above (age range: 65 to 73 years) were treated with Arsenic Trioxide Injection at the recommended dose. A literature review included an additional 4 patients treated with arsenic trioxide for relapsed or refractory APL with ages ranging from 69 to 72 years. No differences in efficacy and safety were observed by age.

8.6 Patients with Renal Impairment

Exposure of arsenic trioxide may be higher in patients with severe renal impairment *[see Clinical Pharmacology (12.3)]*. Patients with severe renal impairment (creatinine clearance less than 30 mL/min) should be monitored for toxicity when these patients are treated with Arsenic Trioxide Injection, and a dose reduction may be warranted.

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

8.7 Patients with Hepatic Impairment

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

10 OVERDOSAGE

10.1 Manifestations

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

10.2 Management

If symptoms of Arsenic Trioxide Injection overdosage develop, the injection should be immediately discontinued and chelation therapy should be considered.

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 (5 -1 g per day), may be given.

11 DESCRIPTION

Arsenic Trioxide Injection 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:

Arsenic Trioxide Injection is available in single-dose vials containing 10 mg of arsenic trioxide.

Arsenic Trioxide Injection 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. Arsenic Trioxide Injection 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 hydrochloric acid, which is used to adjust the pH to 7.5 - 8.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of Arsenic Trioxide Injection is not completely understood. Arsenic trioxide induces 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.

12.2 Pharmacodynamics

Cardiac Electrophysiology

A dedicated QTc study was not performed with Arsenic Trioxide Injection. However, in a single-arm trial of Arsenic Trioxide Injection (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 Injection infusion, and then returned towards baseline by the end of 8 weeks after Arsenic Trioxide Injection infusion.

12.3 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 Injection 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-h} 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-h} 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 Injection 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, 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with Arsenic Trioxide Injection by intravenous administration *[see Warnings and Precautions (5.4)]*.

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.

14 CLINICAL STUDIES

14.2 Relapsed or Refractory APL

Arsenic Trioxide Injection has been investigated in Study PLRXAS01, an open-label, single-arm trial in 40 relapsed or refractory APL patients, previously treated with an anthracycline and a retinoid regimen. Patients received Arsenic Trioxide Injection 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 Injection ≥ 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 Injection, 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 Injection 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.

15 REFERENCES

1. "Hazardous Drugs", *OSHA*. [Accessed on February 12, 2015 from http://www.osha.gov/SLTC/hazardousdrugs/index.html]

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Arsenic Trioxide Injection is supplied as a sterile, clear, colorless solution in glass, single-dose vials.
NDC 63323-637-10 10 mg/10 mL (1 mg/mL) vial in packages of ten vials.

16.2 Storage and Handling

Store at 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F) (See USP Controlled Room Temperature). Do not freeze.

Arsenic Trioxide Injection is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

17 PATIENT COUNSELING INFORMATION

- Differentiation Syndrome
  Advise patients that symptoms of APL differentiation syndrome include fever, sudden weight gain, dizziness/lightheadedness, labored breathing, and accumulation of fluid in the lungs, heart, and chest. This syndrome is managed by immediate treatment with high-dose corticosteroids. Advise patients to immediately report any of these symptoms.

- ECG Abnormalities – QT Prolongation
  Advise patients that Arsenic Trioxide Injection may cause ECG abnormalities, including QT prolongation. QT prolongation is an increase in the time it takes the heart to relax between beats. If extreme, this prolongation has the potential to cause fainting, irregular heartbeat, or more serious side effects. Advise patients to immediately report any of these symptoms. Advise patients to provide a complete list of current medications as caution should be taken when Arsenic Trioxide Injection is coadministered with other medications that can cause QT prolongation or lead to electrolyte abnormalities.

- Other Side Effects
  Advise patients of the expected adverse reactions of Arsenic Trioxide Injection. Most patients in clinical trials experienced some drug-related toxicity, most commonly leukocytosis, gastrointestinal symptoms (nausea, vomiting, diarrhea, and abdominal pain), fatigue, edema, hyperglycemia, dyspnea, cough, rash or itching, headaches, and dizziness. These adverse reactions have not been observed to be permanent or irreversible, nor do they usually require interruption of therapy. Advise patients to call their physician at the onset of any treatment-related adverse reactions.

- Embryo-Fetal Toxicity
  Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider with a known or suspected pregnancy *[see Warnings and Precautions 5.5 and Use in Specific Populations 8.1)]*. Advise females and males of reproductive potential to use effective contraception during treatment with Arsenic Trioxide Injection. Advise females to use effective contraception for six months and males to use effective contraception for three months after completing treatment with Arsenic Trioxide Injection *[see Use in Specific Populations (8.3)]*.

- Potential Effect on Male Fertility
  Advise male patients of the potential risk to future fertility following treatment with Arsenic Trioxide Injection, as decreased testicular weight and impaired spermatogenesis have been reported in animal studies.

- Lactation
  Advise females to discontinue breastfeeding during treatment with Arsenic Trioxide Injection and for two weeks after treatment with Arsenic Trioxide Injection *[see Use in Specific Populations (8.2)]*.

Manufactured for:
FRESENIUS KABI
Lake Zurich, IL 60047

Made in Italy

www.fresenius-kabi.com/us

451442A
Issued: July 2018