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Trisenox® (arsenic trioxide) Injection

Rx only

For Intravenous Use Only

10 mg/10 mL (1mg/mL) ampule

WARNING

Experienced Physician and Institution: TRISENOX (arsenic trioxide) injection should be administered under the supervision of a physician who is experienced in the management of patients with acute leukemia.

APL Differentiation Syndrome: Some patients with APL treated with TRISENOX have experienced symptoms similar to a syndrome called the retinoic-acid-Acute Promyelocytic Leukemia (RA-APL) or APL differentiation syndrome, characterized by fever, dyspnea, weight gain, pulmonary infiltrates and pleural or pericardial effusions, with or without leukocytosis. This syndrome can be fatal. The management of the syndrome has not been fully studied, but high-dose steroids have been used at the first suspicion of the APL differentiation syndrome and appear to mitigate signs and symptoms. At the first signs that could suggest the syndrome (unexplained fever, dyspnea and/or weight gain, abnormal chest auscultatory findings or radiographic abnormalities), high-dose steroids (dexamethasone 10 mg intravenously BID) should be immediately initiated, irrespective of the leukocyte count, and continued for at least 3 days or longer until signs and symptoms have abated. The majority of patients do not require termination of TRISENOX therapy during treatment of the APL differentiation syndrome.

ECG Abnormalities: Arsenic trioxide can cause QT interval prolongation and complete atrioventricular block. QT prolongation can lead to a torsade de pointes-type ventricular arrhythmia, which can be fatal. The risk of torsade de pointes is related to the extent of QT prolongation, concomitant administration of QT prolonging drugs, a history of torsade de pointes, preexisting QT interval prolongation, congestive heart failure, administration of potassium-wasting diuretics, or other conditions that result in hypokalemia or hypomagnesemia. One patient (also receiving amphotericin B) had torsade de pointes during induction therapy for relapsed APL with arsenic trioxide.

ECG and Electrolyte Monitoring Recommendations: Prior to initiating therapy with TRISENOX, a 12-lead ECG should be performed and serum electrolytes (potassium, calcium, and magnesium) and creatinine should be assessed; preexisting electrolyte abnormalities should be corrected and, if possible, drugs that are known to prolong the QT interval should be discontinued. For QTc greater than 500 msec, corrective measures should be completed and the QTc reassessed with serial ECGs prior to considering using TRISENOX. During therapy with TRISENOX, potassium concentrations should be kept

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above 4 mEq/L and magnesium concentrations should be kept above 1.8 mg/dL. Patients who reach an absolute QT interval value > 500 msec should be reassessed and immediate action should be taken to correct concomitant risk factors, if any, while the risk/benefit of continuing versus suspending TRISENOX therapy should be considered. If syncope, rapid or irregular heartbeat develops, the patient should be hospitalized for monitoring, serum electrolytes should be assessed, TRISENOX therapy should be temporarily discontinued until the QTc interval regresses to below 460 msec, electrolyte abnormalities are corrected, and the syncope and irregular heartbeat cease. There are no data on the effect of TRISENOX on the QTc interval during the infusion.

DESCRIPTION

TRISENOX 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 g.

TRISENOX is available in 10 mL, single-use ampules containing 10 mg of arsenic trioxide. TRISENOX 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. TRISENOX is preservative-free. Arsenic trioxide, the active ingredient, is present at a concentration of 1.0 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.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of TRISENOX 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 PML/RAR-alpha.

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

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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.

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 TRISENOX 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.

Special Populations
Effect of Age, Gender, and Race
The effect of age, gender, or race on the pharmacokinetics of TRISENOX has not been studied.

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 $AUC_{0\text{-}24h}$) was 317 ng·hr/mL on Day 1 of Cycle 1 (see **PRECAUTIONS, Pediatric Use**).

Effect of 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 $AUC_{0\text{-}\infty}$ for As^{III} was comparable among the normal, mild and moderate renal

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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 **PRECAUTIONS**). The use of arsenic trioxide in patients on dialysis has not been studied.

Effect of 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 **PRECAUTIONS**).

Drug Interactions

No formal assessments of pharmacokinetic drug-drug interactions between TRISENOX 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 (see **PRECAUTIONS**).

CLINICAL STUDIES

Clinical Studies Experience

TRISENOX has been investigated in 40 relapsed or refractory APL patients, previously treated with an anthracycline and a retinoid regimen, in an open-label, single-arm, non-comparative study. Patients received 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

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who had relapsed less than one year after treatment with ATRA, there were 18 complete responders (82%). Of the 18 patients receiving TRISENOX ≥ one year from ATRA 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 TRISENOX, 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. Reverse Transcriptase – Polymerase Chain Reaction 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.

Another single center study in 12 patients with relapsed or refractory APL, where patients received TRISENOX (arsenic trioxide) injection doses generally similar to the recommended dose, had similar results with 9 of 12 (75%) patients attaining a CR.

INDICATIONS AND USAGE

TRISENOX is indicated for induction of remission and consolidation in patients with acute promyelocytic leukemia (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.

The response rate of other acute myelogenous leukemia subtypes to TRISENOX has not been examined.

CONTRAINDICATIONS

TRISENOX is contraindicated in patients who are hypersensitive to arsenic.

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WARNINGS (see Boxed WARNING)
TRISENOX should be administered under the supervision of a physician who is experienced in the management of patients with acute leukemia.

APL Differentiation Syndrome (see Boxed WARNING): Nine of 40 patients with APL treated with TRISENOX, at a dose of 0.15 mg/kg, experienced the APL differentiation syndrome (see **Boxed WARNIN**G and **ADVERSE REACTIONS**).

Hyperleukocytosis: Treatment with TRISENOX has been associated with the development of hyperleukocytosis ($\geq 10 \times 10^3$/uL) in 20 of 40 patients. A relationship did not exist between baseline WBC counts and development of hyperleukocytosis nor baseline WBC counts and peak WBC counts. Hyperleukocytosis was not treated with additional chemotherapy. WBC counts during consolidation were not as high as during induction treatment.

QT Prolongation (see Boxed WARNING): QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointes as well as complete heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with TRISENOX were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after TRISENOX infusion, and then returned towards baseline by the end of 8 weeks after TRISENOX infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age.

Complete AV block: Complete AV block has been reported with arsenic trioxide in the published literature including a case of a patient with APL.

Carcinogenesis: Carcinogenicity studies have not been conducted with TRISENOX by intravenous administration. The active ingredient of TRISENOX, arsenic trioxide is a human carcinogen.

Pregnancy: TRISENOX may cause fetal harm when administered to a pregnant woman. Studies in pregnant mice, rats, hamsters, and primates have shown that inorganic arsenicals cross the placental barrier when given orally or by injection. The reproductive toxicity of arsenic trioxide has been studied in a limited manner. 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.

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There are no studies in pregnant women using TRISENOX. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. One patient who became pregnant while receiving arsenic trioxide had a miscarriage. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

Laboratory Tests: The patient's electrolyte, hematologic and coagulation profiles should be monitored at least twice weekly, and more frequently for clinically unstable patients during the induction phase and at least weekly during the consolidation phase. ECGs should be obtained weekly, and more frequently for clinically unstable patients, during induction and consolidation.

Drug Interactions: No formal assessments of pharmacokinetic drug-drug interactions between TRISENOX and other agents have been conducted. Caution is advised when TRISENOX is coadministered with other medications that can prolong the QT interval (e.g., certain antiarrhythmics or thioridazine) or lead to electrolyte abnormalities (such as diuretics or amphotericin B).

Carcinogenesis, Mutagenesis, Impairment of Fertility: See WARNINGS section for information on carcinogenesis. 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 produced an increase in the incidence of chromosome aberrations and micronuclei in bone marrow cells of mice. The effect of arsenic on fertility has not been adequately studied.

Pregnancy: Pregnancy Category D. See **WARNINGS** section.

Nursing Mothers: Arsenic is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from TRISENOX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: There are limited clinical data on the pediatric use of TRISENOX. Of 5 patients below the age of 18 years (age range: 5 to 16 years) treated with TRISENOX, at the recommended dose of 0.15 mg/kg/day, 3 achieved a complete response.

In an additional study, the toxicity profile observed in 13 pediatric patients with APL between the ages of 4 and 20 receiving TRISENOX at 0.15 mg/kg/day was similar to that observed in adult patients (see **ADVERSE REACTIONS**).

Safety and effectiveness in relapsed APL pediatric patients below the age of 4 years have not been studied.

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Patients with Renal Impairment: Exposure of arsenic trioxide may be higher in patients with severe renal impairment (see **CLINICAL PHARMACOLOGY, Special Populations**). Patients with severe renal impairment (creatinine clearance less than 30 mL/min) should be closely monitored for toxicity when these patients are treated with TRISENOX, and a dose reduction may be warranted.

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

Patients with Hepatic Impairment: Since limited data are available across all hepatic impairment groups, caution is advised in the use of TRISENOX in patients with hepatic impairment (see **CLINICAL PHARMACOLOGY, Special Populations**). Patients with severe hepatic impairment (Child-Pugh class C) should be closely monitored for toxicity when these patients are treated with TRISENOX.

ADVERSE REACTIONS

Safety information was available for 52 patients with relapsed or refractory APL who participated in clinical trials of TRISENOX. Forty patients in the Phase 2 study received the recommended dose of 0.15 mg/kg of which 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.

Serious adverse events (SAEs), grade 3 or 4 according to version 2 of the NCI Common Toxicity Criteria, were common. Those SAEs attributed to TRISENOX 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 hyperglycemia (n=2).

The following table describes the adverse events that were observed in patients between the ages of 5 – 73 years treated for APL with TRISENOX at the recommended dose at a rate of 5% or more. Similar adverse event profiles were seen in the other patient populations who received TRISENOX.

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Adverse Events (any grade) Occurring in ≥ 5% of 40 Patients with APL who Received TRISENOX (arsenic trioxide) injection at a dose of 0.15 mg/kg/day

System organ class/Adverse Event	All Adverse Events, Any Grade		Grade 3 & 4 Events	
	n	%	n	%
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		
Injection site edema	4	10		
Weakness	4	10	2	5
Hemorrhage	3	8		
Weight gain	5	13		
Weight loss	3	8		
Drug hypersensitivity	2	5	1	3
Gastrointestinal disorders				
Nausea	30	75		
Anorexia	9	23		
Appetite decreased	6	15		
Diarrhea	21	53		
Vomiting	23	58		
Abdominal pain (lower & upper)	23	58	4	10
Sore throat	14	35		
Constipation	11	28	1	3
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		
Metabolism and nutrition disorders				
Hypokalemia	20	50	5	13
Hypomagnesemia	18	45	5	13
Hyperglycemia	18	45	5	13

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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		
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
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		
Skin & 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		
Cardiac disorders				

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Tachycardia	22	55		
ECG QT corrected interval prolonged > 500 msec	16	40		
Palpitations	4	10		
ECG abnormal other than QT interval prolongation	3	8		
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
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
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		
Vascular disorders				
Hypotension	10	25	2	5
Flushing	4	10		
Hypertension	4	10		
Pallor	4	10		
Psychiatric disorders				
Anxiety	12	30		
Depression	8	20		
Agitation	2	5		
Confusion	2	5		
Ocular disorders				
Eye irritation	4	10		
Blurred vision	4	10		
Dry eye	3	8		

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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		
Reproductive system disorders				
Vaginal hemorrhage	5	13		
Intermenstrual bleeding	3	8		
Ear disorders				
Earache	3	8		
Tinnitus	2	5		

The following additional adverse events were reported as related to TRISENOX treatment in 13 pediatric patients (defined as ages 4 through 20): gastrointestinal (dysphagia, mucosal inflammation/stomatitis, oropharyngeal pain, caecitis), metabolic and nutrition disorders (hyponatremia, hypoalbuminemia, hypophosphatemia, and lipase increased), cardiac failure congestive, respiratory (acute respiratory distress syndrome, lung infiltration, pneumonitis, pulmonary edema, respiratory distress, capillary leak syndrome), neuralgia, and enuresis. Pulmonary edema (n=1) and caecitis (n=1) were considered serious reactions.

Post-Marketing Experience
The following reactions have been reported from clinical trials and/or world-wide post-marketing 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, and ventricular tachycardia in association with QT prolongation
Nervous system disorders: peripheral neuropathy
Hematologic disorders: pancytopenia
Respiratory, thoracic, and mediastinal disorders: A differentiation syndrome, like retinoic acid syndrome, has been reported with the use of TRISENOX for the treatment of malignancies other than APL. See Boxed WARNING.

OVERDOSAGE
If symptoms suggestive of serious acute arsenic toxicity (e.g., convulsions, muscle weakness and confusion) appear, TRISENOX (arsenic trioxide) 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 (≤ 1 g per day), may be given.

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DOSAGE AND ADMINISTRATION

TRISENOX should be diluted 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 ampule. The TRISENOX ampule is single-use and does not contain any preservatives. Unused portions of each ampule should be discarded properly. Do not save any unused portions for later administration. Do not mix TRISENOX with other medications.

TRISENOX should be administered intravenously over 1-2 hours. The infusion duration may be extended up to 4 hours if acute vasomotor reactions are observed. A central venous catheter is not required.

Stability

After dilution, TRISENOX is chemically and physically stable when stored for 24 hours at room temperature and 48 hours when refrigerated.

Dosing Regimen

TRISENOX is recommended to be given according to the following schedule:

Induction Treatment Schedule: TRISENOX should be administered intravenously at a dose of 0.15 mg/kg daily until bone marrow remission. Total induction dose should not exceed 60 doses.

Consolidation Treatment Schedule: Consolidation treatment should begin 3 to 6 weeks after completion of induction therapy. TRISENOX should be administered intravenously at a dose of 0.15 mg/kg daily for 25 doses over a period up to 5 weeks.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-4] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

TRISENOX (arsenic trioxide) injection is supplied as a sterile, clear, colorless solution in 10 mL glass, single-use ampules.

NDC 63459-600-10 10 mg/10 mL (1 mg/mL) ampule in packages of ten ampules.

Store at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F). Do not freeze.

Do not use beyond expiration date printed on the label.

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