CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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FINAL PRINTED LABELING

APPROVED

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TRISENOX™ **Rx only**

(arsenic trioxide) injection

For Intravenous Use Only

10 mg/10 mL (1 mg/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 pointe 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 above 4 mEq/dL 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 trixoide 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 7.0 - 9.0.

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 pharmacokinetics of trivalent arsenic, the active species of TRISENOX™, has not been characterized.

Metabolism

The metabolism of arsenic trioxide involves reduction of pentavalent arsenic to trivalent arsenic by arsenate reductase and methylation of trivalent arsenic to monomethylarsonic acid and monomethylarsonic acid to dimethylarsinic acid by methyltransferases. The main site of methylation reactions appears to be the liver. Arsenic is stored mainly in liver, kidney, heart, lung, hair and nails.

Excretion

Disposition of arsenic following intravenous administration has not been studied. Trivalent arsenic is mostly methylated in humans and excreted in urine.

Special Populations

The effects of renal or hepatic impairment or gender, age and race on the pharmacokinetics of TRISENOX™ have not been studied (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. (see PRECAUTIONS).

Clinical Studies

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 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, thirty-one 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, eighteen 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™ doses generally similar to the recommended dose, had similar results with 9 of 12 (75%) patients attaining a CR.

INDICATIONS

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.

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 box WARNING and ADVERSE REACTIONS).

Hyperleukocytosis: Treatment with TRISENOX™ has been associated with the development of hyperleukocytosis ($\geq 10 \times 10^3/\mu L$) 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.

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 fibroblasts, 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.

Safety and effectiveness in pediatric patients below the age of 5 years have not been studied.

Patients with Renal or Hepatic Impairment: Safety and effectiveness of TRISENOX™ in patients with renal and hepatic impairment have not been studied. Particular caution is needed in patients with renal failure receiving TRISENOX™, as renal excretion is the main route of elimination of arsenic.

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 29 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 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™.

Adverse Events (any grade) Occurring in ≥5% of 40 Patients with APL who Received TRISENOX™ 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	40		
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		

Adverse Events (any grade) Occurring in ≥5% of 40 Patients with APL who Received TRISENOX™ 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	%
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
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
Parasthesia	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	2
Ecchymosis	8	20		
Dry Skin	6	13		

Adverse Events (any grade) Occurring in ≥5% of 40 Patients with APL who Received TRISENOX™ 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	%
Erythema- non-specific	5	10		
Increased sweating	5	10		
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				
Tachycardia	22	55		
ECG QT corrected interval prolonged > 500msec	16	38		
Palpitations	4	10		
ECG abnormal other than QT interval prolongation	3	7		
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	14	2	5
Thrombocytopenia	7	19	5	12

Adverse Events (any grade) Occurring in ≥5% of 40 Patients with APL who Received TRISENOX™ 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	%
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		
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		

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

TRISENOX™ should be diluted with 100 to 250mL 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. [1-7] 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 60553-111-10 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.

REFERENCES

1. *Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs.* Publication NIH 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.
2. Council on Scientific Affairs. Guidelines for handling parenteral antineoplastics. *JAMA.* 1985; 253:1590-1592.
3. National Study Commission on Cytotoxic Exposure. *Recommendations for handling cytotoxic agents.* Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Australia.* 1983;1:426-428.
5. Jones RB, et al. Safe handling of chemotherapeutic agents: a report from the Mount Sinai Medical Center. *CA J Clin.* 1983;33:258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm.* 1990; 47:1033-1049.
7. Controlling Occupational Exposure to Hazardous Drugs (OSHA Work-Practice Guidelines). *Am J Health-Syst Pharm.* 1996;53:1669-1685.

Rx only

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