## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use TRISENOX safely and effectively. See full prescribing information for TRISENOX.**

**TRISENOX® (arsenic trioxide) injection, for intravenous administration**
**Initial U.S. Approval: 2000**

**WARNING: APL DIFFERENTIATION SYNDROME, CARDIAC CONDUCTION ABNORMALITIES, AND ELECTROLYTE MONITORING**

***See full prescribing information for complete boxed warning.***

- **Patients have experienced symptoms similar to retinoic-acid-Acute Promyelocytic Leukemia or APL differentiation syndrome, which can be fatal. If symptoms occur, initiate high-dose steroids immediately and continue for at least 3 days until symptoms have abated.**
- **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.**
- **Before intiating therapy, perform a 12-lead ECG, assess serum electrolytes and creatinine, correct preexisting electrolyte abnormalities, and consider discontinuing drugs known to prolong QT interval.**

**----------INDICATIONS AND USAGE----------**

TRISENOX is an arsenical 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.

**----------DOSAGE AND ADMINISTRATION----------**

- For induction therapy, administer intravenously at a dose of 0.15 mg/kg daily until bone marrow remission. Do not exceed 60 doses for total induction. (2.1)
- Begin consolidation treatment 3 to 6 weeks after completion of induction therapy. Administer intravenously at a dose of 0.15 mg/kg daily for 25 doses over a period up to 5 weeks. (2.1)
- Delay treatment for severe non-hematologic adverse reactions. (2.2)
- Dilute prior to use. (2.3)
- Administer intravenously over 1-2 hours. The infusion duration may be extended up to 4 hours if acute vasomotor reactions are observed. (2.3)

**----------DOSAGE FORMS AND STRENGTHS----------**

Injectable solution for intravenous administration supplied as 10 mg/10 ml of arsenic trioxide in single-use ampules. (3)

**----------CONTRAINDICATIONS----------**

Hypersensitivity to arsenic. (4)

**----------WARNINGS AND PRECAUTIONS----------**

- Cardiac Conduction Abnormalities: During TRISENOX therapy, maintain potassium, concentrations above 4 mEq/L and magnesium concentrations above 1.8 mg/dL. (5.2)
- Carcinogenesis: Arsenic trioxide is a human carcinogen. Monitor patients for the development of second primary malignancies. (5.3)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.4, 8.1, 8.3)
- Laboratory Tests: Monitor patient's electrolyte, hematologic and coagulation profiles and obtain ECGs. (5.5)

**----------ADVERSE REACTIONS----------**

The most common adverse reactions in patients with relapsed or refractory APL were leukocytosis, gastrointestinal (nausea, vomiting, diarrhea, and abdominal pain), fatigue, edema, hyperglycemia, dyspnea, cough, rash or itching, headaches, and dizziness. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals USA, Inc. at 1-800-896-5855 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**----------USE IN SPECIFIC POPULATIONS----------**

- Lactation: Discontinue breastfeeding. (8.2)
- Renal Impairment: Monitor patients with severe renal impairment (creatinine clearance less than 30 mL/min) for toxicity when treated with TRISENOX; dose reduction may be warranted. (8.6)
- Hepatic Impairment: Monitor patients with severe hepatic impairment (Child-Pugh Class C) for toxicity when treated with TRISENOX. (8.7)

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 02/2015**

**FULL PRESCRIBING INFORMATION: CONTENTS***



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

**FULL PRESCRIBING INFORMATION**

**WARNING: APL DIFFERENTIATION SYNDROME, CARDIAC CONDUCTION ABNORMALITIES, AND ELECTROLYTE MONITORING**

**APL Differentiation Syndrome:** 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. High-dose steroids have been administered 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), immediately initiate high-dose steroids (dexamethasone 10 mg intravenously BID) , irrespective of the leukocyte count, and continue 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 *[see Warnings and Precautions (5.1)]*.

**Cardiac Conduction Abnormalities:** Before initiating therapy, perform a 12-lead ECG, assess serum electrolytes and creatinine, correct preexisting electrolyte abnormalities, and consider discontinuing drugs known to prolong QT interval. 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 *[see Warnings and Precautions (5.2)]*.

## 1 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.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosage

Induction Treatment Schedule: Administer TRISENOX intravenously at a dose of 0.15 mg/kg daily until bone marrow remission. Do not exceed 60 doses for induction.

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

### 2.2 Dose Adjustment for Non-Hematologic Adverse Reactions

If a severe non-hematologic adverse reaction occurs (such as neurologic or dermatologic toxicity), consider delaying TRISENOX infusion until the event has resolved (≤ Grade 1).

### 2.3 Instructions for Preparation and Intravenous Administration

*Administration*

Administer TRISENOX 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.

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

*Reconstitution*

Dilute TRISENOX 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. Do not save any unused portions for later administration.

*Safe Handling Procedures*

TRISENOX is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

### 2.4 Stability

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

## 3 DOSAGE FORMS AND STRENGTHS

TRISENOX is an injectable solution for intravenous administration supplied as 10mg /10 ml of arsenic trioxide in single-use ampules.

## 4 CONTRAINDICATIONS

TRISENOX is contraindicated in patients who are hypersensitive to arsenic.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 APL Differentiation Syndrome

Nine of 40 patients with APL treated with TRISENOX, at a dose of 0.15 mg/kg, experienced the APL differentiation syndrome. High-dose steroids have been administered 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. *[see Adverse Reactions (6)]*.

### 5.2 Cardiac Conduction Abnormalities: Torsade de Pointes, Complete Heart Block, and QT Prolongation

Torsade de pointes and complete heart block have been reported. QT/QTc prolongation can occur. 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.

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. If it's not possible to discontinue the interacting drug, perform cardiac monitoring frequently *[see Drug Interactions (7)]*.

Monitor ECG weekly, and more frequently for clinically unstable patients.

For QTc greater than 500 msec, complete corrective measures and reassess the QTc with serial ECGs prior to initiating TRISENOX. During TRISENOX therapy, maintain potassium concentrations above 4 mEq/L and magnesium concentrations above 1.8 mg/dL. Reassess patients who reach an absolute QT interval value > 500 msec and immediately correct concomitant risk factors, if any, while the risk/benefit of continuing versus suspending TRISENOX therapy should be considered. There are no data on the effect of TRISENOX on the QTc interval during the infusion.

The risk may be increased when TRISENOX is coadministered with medications that can lead to electrolyte abnormalities (such as diuretics or amphotericin B) *[see Drug Interactions (7)]*.

### 5.3 Carcinogenesis

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

### 5.4 Embryo-Fetal Toxicity

TRISENOX 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 TRISENOX *[*see *Use in Specific Populations (8.1,8.3)]*.

### 5.5 Laboratory Tests

The patient's electrolyte and glucose levels, as well as hepatic, renal, 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.

## 6 ADVERSE REACTIONS

The following serious adverse reactions have been associated with TRISENOX in clinical trials and are discussed in greater detail in other sections of the label.

- APL Differentiation Syndrome *[see Warnings and Precautions (5.1)]*
- Cardiac Conduction Abnormalities: Torsade de Pointes, Complete Heart Block, and QT Prolongation *[see Warnings and Precautions (5.2)]*
- Carcinogenesis *[see Warnings and Precautions (5.3)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.4)]*
- Laboratory Tests *[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.

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 3/4 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).

Table 1 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.

**Table 1**
**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**<br>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 |
| 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** | | | | |
| 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 | | |
| 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.

### 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, and ventricular tachycardia in association with QT prolongation.

**Nervous system disorders:** peripheral neuropathy

**Hematologic disorders:** pancytopenia

**Investigations:** gamma-glutamyltransferase increased

**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]*.

## 7 DRUG INTERACTIONS

*Drugs That Can Prolong the QT/QTc Interval*

Concomitant use of these drugs and TRISENOX 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 TRISENOX. 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 TRISENOX.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

*Risk Summary*

TRISENOX 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 [*see Data*]. A related trivalent arsenic, sodium arsenite, produced teratogenicity when administered during gestation in mice at a dose approximately 5 times the projected human dose on a mg/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 in pregnant women using TRISENOX. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

*Data*

Human Data

One patient who became pregnant while receiving arsenic trioxide had a miscarriage.

Animal Data

Studies in pregnant mice, rats, hamsters, and primates have shown that inorganic arsenicals cross the placental barrier when given orally or by injection. An increase in resorptions, neural-tube defects, anophthalmia and microphthalmia were observed in rats administered 10 mg/kg of arsenic trioxide on gestation day 9 (approximately 10 times the recommended human daily dose on a mg/m² 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/m² 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/m² basis) on gestation day 7 (the lowest dose tested) resulted in neural-tube defects in hamsters.

### 8.2 Lactation

Arsenic is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from TRISENOX, discontinue breastfeeding during treatment with TRISENOX.

### 8.3 Females and Males of Reproductive Potential

*Contraception*

Females

TRISENOX can cause fetal harm when administered to a pregnant woman *[*see *Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during and after treatment with TRISENOX.

Males

Males with female sexual partners of reproductive potential should use effective contraception during and after treatment with TRISENOX.

### 8.4 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 (6.1)]*. No children less than 4 years of age were enrolled in the trial due to the rarity of APL in this age group.

### 8.5 Geriatric Use

Clinical trials of TRISENOX (arsenic trioxide) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Monitor elderly patients closely,

reflecting the greater frequency of decreased hepatic and renal function, concomitant disease or other drug therapy in this population.

### 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 TRISENOX, and a dose reduction may be warranted.

The use of TRISENOX 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 TRISENOX in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*. Monitor patients with severe hepatic impairment (Child-Pugh Class C) who are treated with TRISENOX for toxicity.

## 10 OVERDOSAGE

### 10.1 Manifestations

Manifestations of TRISENOX (arsenic trioxide) overdosage include convulsions, muscle weakness and confusion.

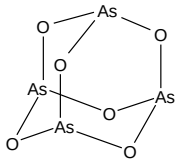
### 10.2 Management

If symptoms of TRISENOX (arsenic trioxide) 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 (≤ 1 g per day), may be given.

## 11 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 and has the following structural formula:




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.

## 12 CLINICAL PHARMACOLOGY

### 12.1 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 promyelocytic leukemia (PML)-retinoic acid receptor (RAR)-alpha.

### 12.2 Pharmacodynamics

*Cardiac Electrophysiology*

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

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.

Renal Impairment

The effect of renal impairment on the pharmacokinetics of $As^{III}$, $As^{V}$, and the pentavalent metabolites $MMA^{V}$ and $DMA^{V}$ was evaluated in 20 patients with advanced malignancies. Patients were classified as having normal renal function (creatinine clearance [CrCl] > 80 mL/min, n=6), mild renal impairment (CrCl 50-80 mL/min, n=5), moderate renal impairment (CrCl 30-49 mL/min, n=6), or severe renal impairment (CrCl < 30 mL/min, n=3). Following twice weekly administration of 0.15 mg/kg over a 2-hour infusion, the mean $AUC_{0-\infty}$ for $As^{III}$ was comparable among the normal, mild and moderate renal impairment groups. However, in the **severe** renal impairment group, the mean $AUC_{0-\infty}$ for $As^{III}$ was approximately 48% higher than that in the normal group.

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

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 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.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with TRISENOX 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 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.

## 14 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, 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. 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.

Hyperleukocytosis (≥ 10 x $10^3$/uL) developed in 20 of the 40 patients treated. 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.

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.

## 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

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.

### 16.2 Storage And Handling

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

TRISENOX is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

## 17 PATIENT COUNSELING INFORMATION

- APL Differentiation Syndrome

  Advise patients that symptoms of APL differentiation syndrome include fever, sudden weight gain, 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 TRISENOX 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 heart beat, 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 TRISENOX 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 TRISENOX. 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 and after treatment with TRISENOX *[*see *Use in Specific Populations (8.3)]*.

- Lactation

  Advise females to discontinue breastfeeding during treatment with TRISENOX *[see Use in Specific Populations (8.2)]*.

**Rx only**

Distributed by:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

TRISENOX is a trademark of Cephalon, Inc. or its affiliates.

©2000-2015 Cephalon, Inc., a wholly-owned subsidiary of Teva Pharmaceutical Industries Ltd, or its affiliates.

All rights reserved.

TRI-XXX