TRISENOX® (arsenic trioxide) injection
Injection: 12 mg arsenic trioxide in 6 mL in single-dose vial. (3)

CONTRAINDICATIONS

Hypersensitivity to arsenic. (4)

WARNINGS AND PRECAUTIONS

- Hepatotoxicity: Grade ≥3 elevations in hepatic transaminase elevation have occurred in patients with newly diagnosed low or intermediate risk APL treated with TRISENOX in combination with tretinoin. Monitor hepatic function tests at least twice weekly during TRISENOX therapy. (5.3)
- Carcinogenesis: Arsenic trioxide is a human carcinogen. Monitor patients for the development of second primary malignancies. (5.4)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.5, 8.1, 8.3)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: DIFFERENTIATION SYNDROME AND CARDIAC CONDUCTION ABNORMALITIES

See full prescribing information for complete boxed warning.

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

RECENT MAJOR CHANGES

Warnings and Precautions (5.6) 12/2018

INDICATIONS AND USAGE

TRISENOX is an arsenical indicated:
- In combination with tretinoin for treatment of adults with newly-diagnosed low-risk acute promyelocytic leukemia (APL) whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression. (1.1)
- For induction of remission and consolidation in patients with APL who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression. (1.2)

DOSE AND ADMINISTRATION

Newly-diagnosed low-risk APL:
- Induction: 0.15 mg/kg intravenously daily in combination with tretinoin until bone marrow remission. Do not exceed 60 days of induction. (2.1)
- Consolidation: 0.15 mg/kg intravenously daily 5 days per week during weeks 1-4 of an 8-week cycle for a total of 4 cycles in combination with tretinoin. (2.1)

Relapsed or refractory APL:
- Induction: 0.15 mg/kg intravenously daily until bone marrow remission. Do not exceed 60 days of total induction. (2.2)
- Consolidation: 0.15 mg/kg intravenously daily for 25 doses over a period up to 5 weeks. (2.2)

8.4 Pediatric Use
8.5 Geriatric Use
8.6 Patients with Renal Impairment
8.7 Patients with Hepatic Impairment

10 OVERDOSAGE
10.1 Manifestations
10.2 Management

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
14.1 Newly-Diagnosed Low-Risk APL
14.2 Relapsed or Refractory APL

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage and Handling

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
1. INDICATIONS AND USAGE

1.1. Newly-Diagnosed Low-Risk APL

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

1.2. Relapsed or Refractory APL

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

2. DOSAGE AND ADMINISTRATION

2.1. Recommended Dosage

Newly-Diagnosed Low-Risk Acute Promelocytic Leukemia (APL)

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

- For the induction cycle, the recommended dose of TRISENOX is 0.15 mg/kg intravenously daily in combination with tretinoin until bone marrow remission and not to exceed 60 days (see Table 1).

- For the consolidation cycles, the recommended dose of TRISENOX is 0.15 mg/kg intravenously daily 5 days per week during weeks 1-4 of an 8-week cycle for a total of 4 cycles in combination with tretinoin (see Table 1). Omit tretinoin during weeks 5-6 of the fourth cycle of consolidation.

Table 1: Recommended Dose of TRISENOX in Combination with Tretinoin

<table>
<thead>
<tr>
<th>Cycle</th>
<th>TRISENOX (0.15 mg/kg)</th>
<th>Tretinoin (22.5 mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>once daily intravenously</td>
<td>twice daily orally until marrow remission but not to exceed 60 days</td>
</tr>
<tr>
<td>Consolidation</td>
<td>once daily intravenously</td>
<td>twice daily orally until marrow remission but not to exceed 60 days</td>
</tr>
</tbody>
</table>

2.2. Dose Modifications for Toxicities

During induction therapy, monitor coagulation studies, blood counts, and chemistries at least 2-3 times per week through recovery. During consolidation, monitor at least weekly. Management of some adverse reactions may require dose interruption, dose reduction, or permanent discontinuation of TRISENOX (see Warnings and Precautions (5.1) and Adverse Reactions (6.1)). Table 2 shows the dose modifications for toxicity due to TRISENOX when used alone or in combination with tretinoin.

Table 2: Dose Adjustments for Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction(s)</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc Prolongation greater than 450 msec for men or greater than 460 msec for women:</td>
<td>Temporarily withhold TRISENOX. Consider holding tretinoin if symptoms are severe.</td>
</tr>
<tr>
<td>Hepatotoxicity, defined by 1 or more of the following:</td>
<td>Withhold treatment with TRISENOX and any medication known to prolong the QTc interval.</td>
</tr>
<tr>
<td>- Total bilirubin (TB) greater than 3 times the upper limit of normal (ULN)</td>
<td>Replete electrolytes.</td>
</tr>
<tr>
<td>- Aspartate aminotransferase (AST) greater than 5 times the ULN</td>
<td>After the QTc normalizes, resume treatment with TRISENOX at a 50% reduced dose (0.075 mg/kg once daily) for 7 days.</td>
</tr>
<tr>
<td>- Alkaline phosphatase (AP) greater than 5 times the ULN</td>
<td>If the 50% reduced dose is tolerated for 7 days (in the absence of QTc prolongation), increase the dose of TRISENOX to 0.11 mg/kg once daily for 7 days.</td>
</tr>
<tr>
<td>- Aspartate aminotransferase (AST) greater than 5 times the ULN</td>
<td>The dose of TRISENOX can be increased to 0.15 mg/kg in the absence of QTc prolongation during that 14-day dose-escalation period.</td>
</tr>
<tr>
<td>Other severe or life-threatening (grade 3-4) nonhematologic reactions</td>
<td>Withhold treatment with TRISENOX and tretinoin.</td>
</tr>
<tr>
<td>- Myelosuppression, defined by 1 or more of the following:</td>
<td>Resume treatment at a 50% reduced dose of the withheld drug(s) when the WBC is less than 1.5 times the ULN and AP/AST are less than 3 times the ULN.</td>
</tr>
<tr>
<td></td>
<td>Increase the dose of the withheld drug(s) back to the recommended dosage after 7 days on the reduced dose in the absence of worsening of hepatotoxicity.</td>
</tr>
<tr>
<td></td>
<td>Discontinue the withheld drug(s) permanently if hepatotoxicity recurs.</td>
</tr>
<tr>
<td>- Leukocytosis (WBC count greater than 10 G/L)</td>
<td>Temporarily withhold TRISENOX and tretinoin.</td>
</tr>
<tr>
<td></td>
<td>When the adverse reaction resolves to no more than mild (grade 1), resume TRISENOX and tretinoin reduced by 2 dose levels (see Table 3 below).</td>
</tr>
<tr>
<td>- Myelosuppression, defined by 1 or more of the following:</td>
<td>Reduce the dose of TRISENOX and/or tretinoin by 1 dose level (see Table 3 below).</td>
</tr>
<tr>
<td></td>
<td>Absolute neutrophil count less than 1 G/L.</td>
</tr>
<tr>
<td></td>
<td>Platelets less than 50 G/L lasting more than 3 weeks</td>
</tr>
<tr>
<td></td>
<td>Consider reducing the dose of TRISENOX and tretinoin by 1 dose level (see Table 3 below).</td>
</tr>
<tr>
<td></td>
<td>If myelosuppression lasts ≥ 50 days or occurs on 2 consecutive cycles, assess a marrow aspirate for remission status. If the marrow aspirate is below 10 G/L.</td>
</tr>
</tbody>
</table>

TRISENOX is a trade name for arsenic trioxide.
TRISENOX® (arsenic trioxide) injection

5.3 Hepatotoxicity
In the clinical trials, 44% of patients with newly-diagnosed low-risk APL treated with TRISENOX in combination with tretinoin experienced elevated aspartate aminotransferase (AST), alkaline phosphatase, and/or serum bilirubin. These abnormalities resolved with temporary discontinuation of TRISENOX and/or tretinoin. During treatment with TRISENOX, monitor liver chemistries at least 2-3 times per week through recovery from toxicities. Withholding treatment of TRISENOX and/or tretinoin if elevations in AST, alkaline phosphatase, and/or serum bilirubin occur to greater than 5 times the upper limit of normal [see Dosage and Administration (2.2)].

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

5.5 Embryo-Fetal Toxicity
TRISENOX can cause fetal harm when administered to a pregnant woman. Arsenic trioxide was embryotokic 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)].

5.6 Encephalopathy
Cases of encephalopathy were reported with treatment with arsenic trioxide. Wernicke encephalopathy after arsenic trioxide treatment were reported in patients with vitamin B1 deficiency. Patients at risk of B1 deficiency should be closely monitored for signs and symptoms of encephalopathy after arsenic trioxide initiation. Some cases recovered with vitamin B1 supplementation.

6 ADVERSE REACTIONS
The following serious adverse reactions are described elsewhere in the labeling.

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

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

Newly-Diagnosed Low-Risk APL

The safety evaluation of TRISENOX in combination with tretinoin is based on results from a randomized trial comparing TRISENOX plus tretinoin (n=129) versus chemotherapy plus tretinoin (n=137) in patients with newly-diagnosed APL (Study APL0406 [see Clinical Studies (14.1)]). In the TRISENOX/tretinoin group, 98% of patients completed induction therapy and 89% completed at least three consolidation cycles. In the chemotherapy/tretinoin group, 90% completed induction therapy and 87% completed all courses of consolidation therapy.

Fatal adverse reactions were reported in 1 (1%) patient on the TRISENOX/tretinoin arm and 8 (6%) patients on the chemotherapy/tretinoin arm. TRISENOX/tretinoin was discontinued due to toxicity in 1 patient during induction and in 4 patients during the first three consolidation courses, whereas chemotherapy/tretinoin was discontinued due to toxicity in 4 patients during induction and in 6 patients during consolidation. Serious adverse reactions reported in 25% on the TRISENOX/tretinoin arm and 24% on the chemotherapy/tretinoin arm. The serious adverse reactions reported in ≥ 2% of patients receiving TRISENOX/tretinoin were abnormal liver tests, differentiation syndrome, dyspnea, pneumonia, and other infections.

Selected hematologic and nonhematologic toxicities that occurred during induction or consolidation are presented in Table 4 for the 129 patients treated with TRISENOX plus tretinoin and the 137 patients treated with chemotherapy plus tretinoin.

Table 4: Selected Adverse Reactions of Trioxin in Combination with Tretinoin in Patients with Newly-Diagnosed APL

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Induction n (%)</th>
<th>First Consolidation n (%)</th>
<th>Second Consolidation n (%)</th>
<th>Third Consolidation n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia&gt; 15 days (Grade 3-4)</td>
<td>TRISENOX/tretinoin 74 (58%) Chemotherapy/tretinoin 120 (88%)</td>
<td>TRISENOX/tretinoin 86 (64%) Chemotherapy/tretinoin 125 (70%)</td>
<td>TRISENOX/tretinoin 6 (5%) Chemotherapy/tretinoin 27 (17%)</td>
<td>TRISENOX/tretinoin 9 (7%) Chemotherapy/tretinoin 26 (16%)</td>
</tr>
<tr>
<td>Neutropenia &gt; 15 days (Grade 3-4)</td>
<td>TRISENOX/tretinoin 61 (48%) Chemotherapy/tretinoin 109 (80%)</td>
<td>TRISENOX/tretinoin 8 (7%) Chemotherapy/tretinoin 40 (32%)</td>
<td>TRISENOX/tretinoin 7 (6%) Chemotherapy/tretinoin 90 (73%)</td>
<td>TRISENOX/tretinoin 5 (4%) Chemotherapy/tretinoin 28 (24%)</td>
</tr>
</tbody>
</table>

TRISENOX® (arsenic trioxide) injection

2.3 Instructions for Preparation and Intravenous Administration

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 vial. Do not save any unused portions for later administration.

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

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS

Injection: 12 mg arsenic trioxide in 6 mL clear solution in a single-dose vial

4 CONTRAINDICATIONS

TRISENOX is contraindicated in patients who are hypersensitive to arsenic.

5 WARNINGS AND PRECAUTIONS

5.1 Differentiation Syndrome

Differentiation syndrome, which may be life-threatening or fatal, has been observed in patients with acute promyelocytic leukemia (APL) treated with TRISENOX. In clinical trials, 16-23% of patients treated with TRISENOX for APL developed differentiation syndrome. Symptoms include unexplained fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusion, weight gain, peripheral edema, hypotension, renal insufficiency, hepatopathy and multi-organ dysfunction. Differentiation syndrome has been observed with and without concomitant hyperleukocytosis, and it has occurred as early as day 1 of induction to as late as the second month induction therapy. When TRISENOX is used in combination with tretinoin, prednisone prophylaxis is advised [see Dosage and Administration (2.1)].

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

5.2 Cardiac Conduction Abnormalities

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

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

Prior to initiating therapy with TRISENOX, assess the QTc interval by electrocardiogram, correct pre-existing electrolyte abnormalities, and consider discontinuing drugs known to prolong QTc interval. Do not administer TRISENOX to patients with ventricular arrhythmias or prolonged QTc interval if possible, discontinue drugs that are known to prolong the QTc interval. If it is not possible to discontinue the interacting drug, perform cardiac monitoring frequently [see Drug Interactions (7)]. During TRISENOX therapy, maintain potassium concentrations above 4 mEq/L and magnesium concentrations above 1.6 mg/dL. Monitor ECG weekly, and more frequently for clinically unstable patients. For patients at risk of QTc prolongation, immediately withhold treatment with TRISENOX and any medication known to prolong the QTc interval. Correct electrolyte abnormalities. When the QTc normalizes, resume TRISENOX at a reduced dose [see Dosage and Administration (2.2)].
### Relapsed or Refractory APL

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 whom 28 completed both induction and consolidation treatment cycles. An additional 12 patients with relapsed or refractory APL received doses generally similar to the recommended dose. Most patients experienced some drug-related toxicity, most commonly leukocytosis, gastrointestinal (nausea, vomiting, diarrhea, and abdominal pain), fatigue, edema, hyperglycemia, dyspnea, cough, rash or itching, headaches, and dizziness. These adverse effects have not been observed to be permanent or irreversible nor do they usually require interruption of therapy. SAEs, Grade ≥3 according to version 2 of the NCI Common Toxicity Criteria, were common. Those SAEs attributed to TRISENOX in the Phase 2 study of 40 patients were 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. 

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

<table>
<thead>
<tr>
<th>Body System</th>
<th>Any Grade Adverse Reactions</th>
<th>Grade ≥3 Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n  %</td>
<td>n  %</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>30</td>
<td>75</td>
</tr>
<tr>
<td>Abdominal pain (lower &amp; upper)</td>
<td>23</td>
<td>58</td>
</tr>
<tr>
<td>Vomiting</td>
<td>23</td>
<td>58</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21</td>
<td>53</td>
</tr>
<tr>
<td>Sore throat</td>
<td>14</td>
<td>35</td>
</tr>
<tr>
<td>Constipation</td>
<td>11</td>
<td>28</td>
</tr>
<tr>
<td>Anorexia</td>
<td>9</td>
<td>23</td>
</tr>
<tr>
<td>Appetite decreased</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>Loose stools</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Oral blistering</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>22</td>
<td>55</td>
</tr>
<tr>
<td>ECG QT corrected interval prolonged &gt; 500 msec</td>
<td>16</td>
<td>40</td>
</tr>
<tr>
<td>Palpitations</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>ECG abnormal other than QT interval prolongation</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td>18</td>
<td>45</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>18</td>
<td>45</td>
</tr>
<tr>
<td>ALT increased</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>AST increased</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Acidosis</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td><strong>Hematologic disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>20</td>
<td>50</td>
</tr>
</tbody>
</table>


*Mostly cases of reversible peripheral neuropathy*
### 6.2 Postmarketing Experience

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

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

#### Nervous system disorders:
- Peripheral neuropathy, paresthesias, seizures, confusion, encephalopathy

#### Hematologic disorders:
- Pancytopenia, bone marrow necrosis

#### Infections and infestations:
- Herpes zoster

#### Toxic epidermal necrolysis

### 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.

#### Drugs That Can Lead to Hepatotoxicity

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

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Risk Summary**

Based on the mechanism of action [see Clinical Pharmacology (12.1)] and findings in animal studies, TRISENOX can cause fetal harm when administered to a pregnant woman. Arsenic trioxide was embryotoxic 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 an equivalent dose of arsenic trioxide. There are no studies with the use of TRISENOX in pregnant women, and limited published data on arsenic trioxide use during pregnancy are insufficient to inform a drug-associated risk of major birth defects and miscarriage. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2.4% and 15-20%, respectively.

**Data**

**Human Data**

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

Animal Data
Studies in pregnant mice, rats, hamsters, and primates have shown that inorganic 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
Risk Summary
Arsenic trioxide is excreted in human milk. There is no information on the effects of arsenic trioxide on the breastfed child or on milk production. Because of the potential for serious adverse reactions in a breastfed child from TRISENOX, discontinue breastfeeding during treatment with TRISENOX and for two weeks after the final dose.

8.3 Females and Males of Reproductive Potential

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

Contraception
Females
Advise females of reproductive potential to use effective contraception during and after treatment with TRISENOX and for six months after the final dose.

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

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

8.4 Pediatric Use

The safety and efficacy of TRISENOX in combination with tretinoin in pediatric patients has not been established.

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

8.5 Geriatric Use

Use of TRISENOX in combination with tretinoin in newly-diagnosed adult patients with low-risk APL is supported by a randomized, controlled trial that included 16 patients between the ages of 60 and 70 years. No differences in efficacy and safety were observed by age. A literature review included an additional 77 patients treated with arsenic trioxide in combination with tretinoin as part of induction and consolidation therapy for low and high risk APL, with ages ranging from 60 to 84 years. These studies showed lower survival rates in older patients. Monitor elderly patients frequently during treatment with TRISENOX.

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

8.6 Patients with Renal Impairment

Exposure of arsenic trioxide may be higher in patients with severe renal impairment [see Clinical Pharmacology (12.3)]. Patients with severe renal impairment (creatinine clearance less than 30 mL/min) should be monitored for toxicity when these patients are treated with 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 administration at a dose of 3 mg/kg intramuscularly every 4 hours until immediately 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 As₂O₃, with a molecular weight of 197.8 and has the following structural formula:

TRISENOX is available in 10 mL, single-dose vials containing 12 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 2 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 declining 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 As³⁺ (mean AUC₉₋₁₅) 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, MMA³⁺ and DMA³⁺, 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 As³⁺. The mean estimated terminal elimination half-lives of the metabolites MMA³⁺ and DMA³⁺ 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. As³⁺ is present in plasma only at relatively low levels.

Distribution
The volume of distribution (V₉₅) for As³⁺ is large (mean 562 L, N=10) indicating that As³⁺ is widely distributed throughout body tissues. V₉₅ is also dependent on body weight and increases as body weight increases.

Elimination

Metabolism

Most of the As³⁺ is distributed to the tissues where it is methylated to the less cyaotoxic metabolites, monomethylarsonic acid (MMA³⁺) and dimethylarsinic acid (DMA³⁺) by methyltransferases primarily in the liver. The metabolism of arsenic trioxide also involves oxidation of As³⁺ to As⁵⁺, which may occur in numerous tissues via enzymatic or nonenzymatic processes. As⁵⁺ 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 As³⁺. The methylated metabolites of As³⁺ (MMA³⁺, DMA³⁺) are primarily excreted in the urine. The total clearance of As³⁺ is 49 L/h and the renal clearance is 9 L/h. Clearance is not dependent on body weight or dose administered over the range of 7-32 mg.

Specific Populations

Patients with Renal Impairment

The effect of renal impairment on the pharmacokinetics of As³⁺, As⁵⁺, and the pentavalent metabolites MMA³⁺ and DMA³⁺ was evaluated in 20 patients with advanced
malignancies. Patients were classified as having normal renal function (creatinine clearance
(CrCl) > 90 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_{inf} for As^{III} was comparable among the
normal, mild and moderate renal impairment groups. However, in the severe renal
impairment group, the mean AUC_{inf} for As^{III} was approximately 48% higher than
that in the normal group.

Systemic exposure to MMA\(^{\text{V}}\) and DMA\(^{\text{V}}\) tended to be larger in patients with renal
impairment; however, the clinical consequences of this increased exposure are not
known. MMA\(^{\text{V}}\) plasma levels were generally below the limit of assay quantitation in
patients with mild renal impairment. See Use in Specific Populations (8.7). The use
of arsenic trioxide in patients on dialysis has not been studied.

**Patients with Hepatic Impairment**

The effect of pharmacokinetics of As^{III}, As^{V}, and the pentavalent metabolites MMA\(^{\text{V}}\) and
DMA\(^{\text{V}}\) 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\(^{\text{V}}\) or DMA\(^{\text{V}}\) 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\(_{\text{inf}}\) and \(C_{\text{max}}\) values 40% and 70% higher, respectively,
than those patients with normal hepatic function. The mean dose-normalized trough
plasma levels for both MMA\(^{\text{V}}\) and DMA\(^{\text{V}}\) in this severely hepatically impaired patient
were 2.2- to 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\(_{\text{inf}}\))
was 317 ng·hr/mL on Day 1 of Cycle 1 [see Use in Specific Populations (8.4)].

**Drug Interaction Studies**

No formal assessments of pharmacokinetic drug-drug interactions between TRISENOX
and other drugs have been conducted. The methyltransferases responsible for
metabolizing arsenic trioxide are not members of the cytochrome P450 family of
isozymes, and therefore, arsenic trioxide is not expected to inhibit or induce P450
isoenzymes. In vitro incubation of arsenic trioxide with human liver microsomes
showed no inhibition on the activities of the major cytochrome P450 (CYP) enzymes
such as 1A2, 2E1, 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 kidney cells). Trivalent arsenic was genotoxic in the chromosome
aberrations assay and micronucleus bone marrow assay in mice. The effect of arsenic on fertility has not been adequately studied in humans. Decreased testicular weight and impaired spermatogenesis have been reported in animal studies. Male Wistar rat pups were administered 1.5 mg/kg sodium arsenite solution via
intraperitoneal route from postnatal days 1 to 14 and testes were collected for
analyses. In beagle dogs administered intravenous arsenic trioxide for 90 days, reduced
male Wistar rat pups were administered 1.5 mg/kg sodium arsenite solution via
intraperitoneal route from postnatal days 1 to 14 and testes were collected for
analysis. In beagle dogs administered intravenous arsenic trioxide for 90 days, reduced
testicular weight and impaired spermatogenesis have been reported in animal studies. The male Wistar rat pups were administered 1.5 mg/kg sodium arsenite solution via
intraperitoneal route from postnatal days 1 to 14 and testes were collected for
analysis. In beagle dogs administered intravenous arsenic trioxide for 90 days, reduced
testicular weight and impaired spermatogenesis have been reported in animal studies.

**14 CLINICAL STUDIES**

**14.1 Newly-Diagnosed Low-Risk APL**

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

Patients in the TRISENOX/tretinoin group received induction treatment with
TRISENOX 0.15 mg/kg intravenously once daily in combination with tretinoin 22.5 mg/m² (rounded to the nearest 10 mg increment) orally twice daily 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 concomitant 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
31 patients, there were 18 complete responders (82%). The 81 patients receiving
TRISENOX or one year from tretinoin treatment, there were 10 complete responders
(55%). The median time to bone marrow remission was 44 days and to onset of CR
was 53 days. Three of 5 children, 5 years or older, achieved CR. No children less than
5 years old were treated.

Three to six weeks following bone marrow remission, 31 patients received consolidation
therapy with TRISENOX, at the same dose, for 25 additional days over a period
up to 5 weeks. In follow-up treatment, 18 patients received further TRISENOX 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 7 (71%) patients who met some, but not all, of the response criteria, and in 3 of
7 (43%) of patients who did not respond. RT-PCR conversions to no detection of the
APL gene rearrangement were demonstrated in 22 of 28 (79%) of patients who met
the response criteria, in 3 of 5 (60%) of patients who met some, but not all, of the
response criteria, and in 2 of 7 (29%) of patients who did not respond.

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

**15 REFERENCES**

   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-dose vials.

NDC 63459-601-06 12 mg/6 mL (2 mg/mL) vial in packages of ten vials.

16.2 Storage and Handling
Store at 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F) (See USP Controlled Room Temperature). Do not freeze.
TRISENOX is a cytotoxic drug. Follow applicable special handling and disposal procedures.

17 PATIENT COUNSELING INFORMATION

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

• ECG Abnormalities – QT Prolongation
Advise patients that 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 heartbeat, or more serious side effects. Advise patients to immediately report any of these symptoms. Advise patients to provide a complete list of current medications as caution should be taken when 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 treatment with TRISENOX. Advise females to use effective contraception for six months and males to use effective contraception for three months after completing treatment with TRISENOX [see Use in Specific Populations (8.3)].

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

• Lactation
Advise females to discontinue breastfeeding during treatment with TRISENOX and for two weeks after treatment with TRISENOX [see Use in Specific Populations (8.2)].