TRISENOX® (arsenic trioxide) injection, for intravenous use

Indications and Usage

TRISENOX is an arsenical indicated:

- Relapsed or refractory APL:
- Newly-diagnosed low-risk APL:

\[ \text{Induction: Administer } 0.15 \text{ mg/kg/day intravenously daily in combination with tretinoin until bone marrow remission. Do not exceed 60 days. (2.1)} \]

\[ \text{Consolidation: Administer } 0.15 \text{ mg/kg/day intravenously daily for 5 days per week during weeks 1-4 of each 8-week cycle for a total of 4 cycles in combination with tretinoin. (2.2)} \]

\[ \text{Relapsed or refractory APL:} \]

\[ \text{Induction: Administer } 0.05 \text{ mg/kg/day intravenously daily until bone marrow remission. Do not exceed 60 days. (2.2)} \]

\[ \text{Consolidation: Administer } 0.05 \text{ mg/kg/day intravenously daily for 25 doses over a period of up to 5 weeks. (2.2)} \]

Dosage Forms and Strengths

Injection: 12 mg/6 mL (2 mg/mL) arsenic trioxide in single-dose vial. (3)

Warnings and Precautions

- Hepatotoxicity: Elevated aspartate aminotransferase (AST), alkaline phosphatase and serum bilirubin have occurred in patients with newly-diagnosed low-risk APL treated with TRISENOX in combination with tretinoin. Monitor hepatic function tests at least twice weekly during induction and at least once weekly during consolidation. Withhold TRISENOX for certain elevations in AST, alkaline phosphatase and bilirubin and resume at reduced dose upon resolution. (2.3, 5.4)

- Carcinogenesis: Arsenic trioxide is a human carcinogen. Monitor patients for the development of second primary malignancies. (5.5)

- Embryo-Fetal Toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.6, 8.1, 8.3)

Adverse Reactions

The most common adverse reactions (>30%) are nausea, cough, fatigue, pyrexia, headache, abdominal pain, vomiting, tachycardia, diarrheea, dyspnea, hypokalemia, leukocytosis, hyperglycemia, hypomagnesemia, insomnia, dermatitis, edema, QTc prolongation, rigors, sore throat, arthralgia, paresthesia, and pruritus (6.1).

Use in Specific Populations

- Lactation: Advise not to breastfeed. (8.2)

- Renal Impairment: Monitor patients with severe renal impairment (creatinine clearance less than 30 mL/min) for toxicity when treated with 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: 06/2022

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TRISENOX® (arsenic trioxide) injection

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 for Newly-Diagnosed Low-Risk Acute Promyelocytic 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 dosage of TRISENOX is 0.15 mg/kg/day intravenously in combination with tretinoin until bone marrow remission but not to exceed 60 days (see Table 1).
- For the consolidation cycles, the recommended dosage of TRISENOX is 0.15 mg/kg/day intravenously daily 5 days per week during weeks 1-4 of each 8-week cycle for a total of 4 cycles. Administer tretinoin by 1 dose level (see Table 1). Omit tretinoin during weeks 5-6 of the fourth cycle of consolidation.

Table 1: Recommended Dosage of TRISENOX in Combination with Tretinoin

<table>
<thead>
<tr>
<th>TRISENOX</th>
<th>Tretinoin</th>
<th>Consolation (4 cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.15 mg/kg once daily</td>
<td>until marrow remission but to not exceed 60 days</td>
<td></td>
</tr>
<tr>
<td>22.5 mg/m² twice daily</td>
<td>until marrow remission but to not exceed 60 days</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TRISENOX 0.15 mg/kg once daily intravenously</th>
<th>Tretinoin 22.5 mg/m² twice daily orally</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1-5</td>
<td>Days 1-5</td>
<td>Days 1-5</td>
<td>Days 1-5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Days 1-7</td>
<td>Days 1-7</td>
<td>-</td>
<td>-</td>
<td>Days 3 1-7</td>
<td>Days 1-7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

2.2 Recommended Dosage for Relapsed or Refractory APL

A treatment course for patients with relapsed or refractory APL consists of 1 induction cycle and 1 consolidation cycle (see Clinical Studies (14.2)).

- For the induction cycle, the recommended dosage of TRISENOX is 0.15 mg/kg/day intravenously daily until bone marrow remission or up to a maximum of 60 days.
- For the consolidation cycle, the recommended dosage of TRISENOX is 0.15 mg/kg/day intravenously daily for 25 doses over a period of up to 5 weeks. Begin consolidation 3 to 6 weeks after completion of induction cycle.

3 CLINICAL STUDIES

3.1 Efficacy

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.

3.2 ADVERSE REACTIONS

3.2.1 General adverse reactions

- Rate of differentiation syndrome
- Rate of molecular remission
- Rate of response in relapse

3.2.2 Nonhematologic reactions

- Hypotension
- Leukopenia (absolute neutrophil count less than 1 G/L lasting more than 5 weeks)
- Myelosuppression, defined by 1 or more of the following:
- Absolute neutrophil count less than 1 G/L
- Plateletless less than 50 G/L lasting more than 5 weeks

4 DRUG INTERACTIONS

4.1 Cardiac Drugs

- Correct electrolyte abnormalities.
- If QTc increase does not resolve, decrease the QTc interval.
- If QTc interval exceeds 0.50 s, discontinue TRISENOX.
- If signs of QTc interval prolongation during the dose escalation period, discontinue TRISENOX.
- If signs of QTc interval prolongation persist, permanently discontinue TRISENOX.

4.2 Hepatotoxicity

- Administer Tretinoin and/or tretinoin.
- Administer dexamethasone 10 mg intravenously daily for 25 doses over a period of up to 5 weeks. Begin consolidation 3 to 6 weeks after completion of induction cycle.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiac Conduction Abnormalities

- QTc interval prolongation
- QTc interval prolongation during the dose escalation period
- QTc interval prolongation persist
- QTc interval prolongation
- QTc interval prolongation

5.2 Hepatotoxicity

- Administer Tretinoin and/or tretinoin.
- Administer hydroxyurea.
- Administer dexamethasone 10 mg intravenously daily for 25 doses over a period of up to 5 weeks. Begin consolidation 3 to 6 weeks after completion of induction cycle.

6 ADVERSE REACTIONS

6.1 Nonhematologic reactions

- Hypotension
- Leukopenia (absolute neutrophil count less than 1 G/L lasting more than 5 weeks)
- Myelosuppression, defined by 1 or more of the following:
- Absolute neutrophil count less than 1 G/L
- Plateletless less than 50 G/L lasting more than 5 weeks

7 DOSAGE AND ADMINISTRATION

7.1 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.

8 ADVERSE REACTIONS

8.1 General adverse reactions

- Rate of differentiation syndrome
- Rate of molecular remission
- Rate of response in relapse

8.2 Nonhematologic reactions

- Hypotension
- Leukopenia (absolute neutrophil count less than 1 G/L lasting more than 5 weeks)
- Myelosuppression, defined by 1 or more of the following:
- Absolute neutrophil count less than 1 G/L
- Plateletless less than 50 G/L lasting more than 5 weeks

9 DRUG INTERACTIONS

9.1 Cardiac Drugs

- Correct electrolyte abnormalities.
- If QTc increase does not resolve, decrease the QTc interval.
- If QTc interval exceeds 0.50 s, discontinue TRISENOX.
- If signs of QTc interval prolongation during the dose escalation period, discontinue TRISENOX.
- If signs of QTc interval prolongation persist, permanently discontinue TRISENOX.

10 WARNINGS AND PRECAUTIONS

10.1 Cardiac Conduction Abnormalities

- QTc interval prolongation
- QTc interval prolongation during the dose escalation period
- QTc interval prolongation persist
- QTc interval prolongation
- QTc interval prolongation

11 ADVERSE REACTIONS

11.1 General adverse reactions

- Rate of differentiation syndrome
- Rate of molecular remission
- Rate of response in relapse

11.2 Nonhematologic reactions

- Hypotension
- Leukopenia (absolute neutrophil count less than 1 G/L lasting more than 5 weeks)
- Myelosuppression, defined by 1 or more of the following:
- Absolute neutrophil count less than 1 G/L
- Plateletless less than 50 G/L lasting more than 5 weeks

12 DOSAGE AND ADMINISTRATION

12.1 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.

12.2 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.

13 CLINICAL STUDIES

13.1 Efficacy

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.

13.2 ADVERSE REACTIONS

13.2.1 General adverse reactions

- Rate of differentiation syndrome
- Rate of molecular remission
- Rate of response in relapse

13.2.2 Nonhematologic reactions

- Hypotension
- Leukopenia (absolute neutrophil count less than 1 G/L lasting more than 5 weeks)
- Myelosuppression, defined by 1 or more of the following:
- Absolute neutrophil count less than 1 G/L
- Plateletless less than 50 G/L lasting more than 5 weeks

14 INDICATIONS AND USAGE

14.1 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.

14.2 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.

15 WARNINGS AND PRECAUTIONS

15.1 Cardiac Conduction Abnormalities

- QTc interval prolongation
- QTc interval prolongation during the dose escalation period
- QTc interval prolongation persist
- QTc interval prolongation
- QTc interval prolongation

16 ADVERSE REACTIONS

16.1 General adverse reactions

- Rate of differentiation syndrome
- Rate of molecular remission
- Rate of response in relapse

16.2 Nonhematologic reactions

- Hypotension
- Leukopenia (absolute neutrophil count less than 1 G/L lasting more than 5 weeks)
- Myelosuppression, defined by 1 or more of the following:
- Absolute neutrophil count less than 1 G/L
- Plateletless less than 50 G/L lasting more than 5 weeks

17 DOSAGE AND ADMINISTRATION

17.1 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.

17.2 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.
3. DOSAGE FORMS AND STRENGTHS

Injection: 12 mg/6 mL (2 mg/mL) arsenic trioxide clear solution in a single-dose vial

4. CONTRAINDICATIONS

TRISENOX is contraindicated in patients with hypersensitivity 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. Signs and symptoms include unexplained fever, dyspnea, hypoxia, acute respiratory distress, 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/or without concomitant leukocytosis, 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, prophylaxis with prednisone is recommended during the induction cycle (see Dosage and Administration (2.1)). If differentiation syndrome is suspected, temporarily withhold TRISENOX and immediately initiate dexamethasone 10 mg intravenously every 12 hours and hemodynamic monitoring until resolution of signs and symptoms for a minimum of 3 days (see Dosage and Administration (2.3)).

5.2 Cardiac Conduction Abnormalities

Patients treated with TRISENOX can develop QTc prolongation, torsade de points, and complete atrioventricular block. In the clinical trials of patients with newly-diagnosed low-risk APL treated with TRISENOX in combination with tretinoin, 11% experienced QTc (Framingham formula) prolongation >450 msec for men and >460 msec for women throughout the treatment cycle. 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 torsade de points is related to the extent of QTc prolongation, concomitant administration of QTc prolonging drugs, a history of torsade de points, 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 a ventricular arrhythmia or prolonged QTc. If possible, discontinue drugs that are known to prolong the QTc interval. If it is not possible to discontinue the interacting drug, perform cardiac monitoring frequently (see Drug Interactions (7)). During TRISENOX therapy, maintain potassium concentrations above 4 mEq/L and magnesium concentrations above 4 mM/L and magnesium concentrations above 1.8 mg/dL. Monitor ECG weekly and more frequently for clinically unstable patients.

For patients who develop a QTc Framingham greater than 450 msec for men or greater than 460 msec for women, withhold TRISENOX and any medication known to prolong the QTc interval. Correct electrolyte abnormalities. When the QTc normalizes and electrolyte abnormalities are corrected, resume TRISENOX at a reduced dose (see Dosage and Administration (2.3)).

5.3 Encephalopathy

Serious encephalopathies were reported in patients receiving TRISENOX. Monitor patients for neurological symptoms, such as confusion, decreased level of consciousness, seizures, cognitive deficits, ataxia, visual symptoms and ocular motor dysfunction. Advise patients and caregivers of the need for close observation.

5.4 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.

5.5 Carcinogenesis

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

5.6 Embryo-Fetal Toxicity

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. A related trivalent arsenic, arsenic acid, was produced teratogenically 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 of reproductive potential to use effective contraception during treatment with TRISENOX and for 6 months after the last dose.

5.7 Wernicke's Encephalopathy

Wernicke's encephalopathy occurred in patients receiving TRISENOX. Wernicke's encephalopathy is a neurologic emergency that can be prevented and treated with thiamine. Consider testing thiamine levels in patients at risk for thiamine deficiency (e.g., chronic alcohol use, malabsorption, nutritional deficiency, concomitant use of furosemide). Administer parenteral thiamine in patients with or at risk for thiamine deficiency. Monitor patients for neurological symptoms and nutritional status while receiving TRISENOX. If Wernicke's encephalopathy is suspected, immediately interrupt TRISENOX and initiate parenteral thiamine. Monitor until symptoms resolve or improve and thiamine levels normalize.

6. ADVERSE REACTIONS

The following clinically significant 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))
- Encephalopathy (see Warnings and Precautions (5.3))
- Hepatotoxicity (see Warnings and Precautions (5.4))
- Carcinogenesis (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.

6.2 Newly-Diagnosed Low-Risk APL

The efficacy of TRISENOX in combination with tretinoin was evaluated in Study APL0406, a randomized trial comparing TRISENOX plus tretinoin (n=129) versus chemotherapy plus tretinoin (n=137) in patients with newly-diagnosed APL (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, 96% completed induction therapy and 87% patients completed all three courses of consolidation therapy. Serious adverse reactions were reported in 25% of patients on the TRISENOX/tretinoin arm and 24% on the chemotherapy/tretinoin arm. The serious adverse reactions reported in ≥2% of patients who received TRISENOX/tretinoin were abnormal liver tests, differentiation syndrome, dyspnea, pneumonia, and other infections. 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.

Selected hematologic and nonhematologic toxicities that occurred during induction or consolidation are presented in Table 4.

Table 4: Select Adverse Reactions of TriソNex in Combination with Tretinoin in Patients with Newly-Diagnosed APL in Study APL0406

<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</td>
<td>74 (59%)</td>
<td>120 (88%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>TRISENOX/tretinoin Chemotherapy/tretinoin</td>
<td>61 (48%)</td>
<td>105 (80%)</td>
<td>8 (7%)</td>
<td>40 (32%)</td>
</tr>
</tbody>
</table>

Note: continued
<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>Hepatic toxicity (Grade 3-4)</td>
<td>51 (40%)</td>
<td>5 (4%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>TRISENOX/tretinoin Chemotherapy/tretinoin</td>
<td>4 (3%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Infection and fever of unknown origin</td>
<td>30 (23%)</td>
<td>10 (8%)</td>
<td>4 (3%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>TRISENOX/tretinoin Chemotherapy/tretinoin</td>
<td>75 (55%)</td>
<td>8 (6%)</td>
<td>46 (38%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>29 (22%)</td>
<td>22 (18%)</td>
<td>17 (14%)</td>
<td>16 (14%)</td>
</tr>
<tr>
<td>TRISENOX/tretinoin Chemotherapy/tretinoin</td>
<td>29 (22%)</td>
<td>19 (15%)</td>
<td>10 (8%)</td>
<td>13 (11%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>14 (10%)</td>
<td>19 (16%)</td>
<td>16 (14%)</td>
<td>11 (9%)</td>
</tr>
<tr>
<td>TRISENOX/tretinoin Chemotherapy/tretinoin</td>
<td>12 (9%)</td>
<td>16 (10%)</td>
<td>16 (14%)</td>
<td>11 (9%)</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>11 (9%)</td>
<td>3 (2%)</td>
<td>3 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>TRISENOX/tretinoin Chemotherapy/tretinoin</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Gastrointestinal toxicity (Grade 3-4)</td>
<td>3 (2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>TRISENOX/tretinoin Chemotherapy/tretinoin</td>
<td>25 (18%)</td>
<td>6 (5%)</td>
<td>7 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Neurotoxicity*</td>
<td>1 (1%)</td>
<td>5 (4%)</td>
<td>6 (5%)</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>TRISENOX/tretinoin Chemotherapy/tretinoin</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Cardiac function (Grade 3-4)</td>
<td>5 (4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>TRISENOX/tretinoin Chemotherapy/tretinoin</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*Mostly cases of reversible peripheral neuropathy

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 Study PLRXAS01 received the recommended dose of 0.35 mg/kg, of whom 28 completed both induction and consolidation cycles. An additional 12 patients with relapsed or refractory APL received doses generally similar to the recommended dose.

Serious adverse reactions observed in the 40 patients with refractory or relapsed APL enrolled in Study PLRXAS01 included differentiation syndrome (n =3), hyperleukocytosis (n =3), QTC interval ≥ 500 msec (n=16, 1 with torsade de points), atrial dysrhythmias (n=2), and hyperglycemia (n=2).

The most common adverse reactions (> 30%) were nausea, cough, fatigue, pyrexia, headache, abdominal pain, vomiting, tachycardia, diarrhea, dyspnea, hypokalemia, leukocytosis, hyperglycemia, hypomagnesemia, insomnia, dermatitis, edema, QTC prolongation, rigors, sore throat, arthralgia, paresthesia, and pruritus.

Table 5 describes the adverse reactions in patients aged 5 to 73 years with APL who received TRISENOX at the recommended dose. Similar adverse reactions profiles were seen in the other patient populations who received TRISENOX.

**Table 5: Adverse Reactions (≥ 5%) in Patients with Relapsed or Refractory APL Who Received TRISENOX in Study PLRXAS01**

<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>%</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>Abdominal tenderness</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Diarrhea hemorrhagic</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>26</td>
<td>65</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>21</td>
<td>53</td>
</tr>
</tbody>
</table>

**Nervous system disorders**

- Headache: 24 (60)
- Insomnia: 17 (43)
- Paresthesia: 13 (33)
- Dizziness (excluding vertigo): 9 (23)
- Tremor: 5 (13)
- Convulsion: 3 (8)
- Somnolence: 3 (8)
- Coma: 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)

**Hematologic disorders**

- Leukocytosis: 20 (50)
- Anemia: 8 (20)
- Thrombocytopenia: 7 (18)
- Febrile neutropenia: 5 (13)
- Neutropenia: 4 (10)
- Disseminated intravascular coagulation: 3 (8)
- Lymphadenopathy: 3 (8)

**Skin and subcutaneous tissue disorders**

- Dermatitis: 17 (43)
- Pruritus: 13 (33)
- Ecchymosis: 8 (20)
- Dry skin: 6 (15)

**Metabolism and nutrition disorders**

- Hypokalemia: 20 (50)
- Hypomagnesemia: 18 (45)
- Hyperglycemia: 18 (45)
- ALT increased: 8 (20)
- Hyperkalemia: 7 (18)
- AST increased: 5 (13)
- Hypocalcemia: 4 (10)
- Hypoglycemia: 3 (8)
- Acidosis: 2 (5)

**Drug hypersensitivity**

- Fatigue: 25 (63)
- Pyrexia (fever): 25 (63)
- Edema - non-specific: 16 (40)
- Rigors: 15 (38)
- Chest pain: 10 (25)
- Injection site pain: 8 (20)
- Pain - non-specific: 6 (15)
- Injection site erythema: 5 (13)
- Weight gain: 5 (13)
- Injection site edema: 4 (10)
- Weakness: 4 (10)
- Hemorrhage: 3 (8)
- Weight loss: 3 (8)
- Drug hypersensitivity: 2 (5)

**Respiratory**

- Epistaxis: 10 (25)
- Hypoxia: 9 (23)
- Pleural effusion: 8 (20)
- Wheezing: 5 (13)
- Decreased breath sounds: 4 (10)
- Capitulations: 4 (10)
- Sore throat: 4 (10)
- Hemoptysis: 3 (8)
- Tachypnea: 3 (8)
- Rhonchi: 3 (8)

**General disorders and administration site conditions**

- Fatigue: 25 (63)
- Pyrexia (fever): 25 (63)
- Edema - non-specific: 16 (40)
- Rigors: 15 (38)
- Chest pain: 10 (25)
- Injection site pain: 8 (20)
- Pain - non-specific: 6 (15)
- Injection site erythema: 5 (13)
- Weight gain: 5 (13)
- Injection site edema: 4 (10)
- Weakness: 4 (10)
- Hemorrhage: 3 (8)
- Weight loss: 3 (8)
- Drug hypersensitivity: 2 (5)

**ECG QT corrected interval prolonged**

- Fatigue: 25 (63)
- Pyrexia (fever): 25 (63)
- Edema - non-specific: 16 (40)
- Rigors: 15 (38)
- Chest pain: 10 (25)
- Injection site pain: 8 (20)
- Pain - non-specific: 6 (15)
- Injection site erythema: 5 (13)
- Weight gain: 5 (13)
- Injection site edema: 4 (10)
- Weakness: 4 (10)
- Hemorrhage: 3 (8)
- Weight loss: 3 (8)
- Drug hypersensitivity: 2 (5)
TRISENOX® (arsenic trioxide) injection

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse reaction</th>
<th>Any Grade Adverse Reactions</th>
<th>Grade ≥3 Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Erythema - non-specific</td>
<td>5</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Increased sweating</td>
<td>5</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Facial edema</td>
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<td>8</td>
<td></td>
</tr>
<tr>
<td>Night sweats</td>
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<td></td>
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<tr>
<td>Petechiae</td>
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<tr>
<td>Hyperpigmentation</td>
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<td>8</td>
<td></td>
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<tr>
<td>Non-specific skin lesions</td>
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<td>8</td>
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</tr>
<tr>
<td>Urticaria</td>
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<td>8</td>
<td></td>
</tr>
<tr>
<td>Local exfoliation</td>
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<td>5</td>
<td></td>
</tr>
<tr>
<td>Eyelid edema</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Musculoskeletal, connective tissue, and bone disorders

| Arthralgia | 13 | 33 | 3 | 8 |
| Myalgia | 10 | 25 | 2 | 5 |
| Bone pain | 9 | 23 | 4 | 10 |
| Back pain | 7 | 18 | 1 | 3 |
| Neck pain | 5 | 13 |     |     |
| Pain in limb | 5 | 13 | 2 | 5 |

Psychiatric disorders

| Anxiety | 12 | 30 |     |     |
| Depression | 8 | 20 |     |     |
| Agitation | 2 | 5  |     |     |
| Confusion | 2 | 5  |     |     |

Vascular disorders

| Hypotension | 10 | 25 | 2 | 5 |
| Flushing | 4 | 10 |     |     |
| Hypertension | 4 | 10 |     |     |
| Faller | 4 | 10 |     |     |

Infections and infestations

| Sinusitis | 8 | 20 |     |     |
| Herpes simplex | 5 | 13 |     |     |
| Upper respiratory tract infection | 5 | 13 | 1 | 3 |
| Bacterial infection - non-specific | 3 | 8 | 1 | 3 |
| Herpes zoster | 3 | 8 |     |     |
| Nasopharyngitis | 2 | 5 |     |     |
| Oral candidiasis | 2 | 5 |     |     |
| Sepsis | 2 | 5 | 2 | 5 |

Reproductive system disorders

| Vaginal hemorrhage | 5 | 13 |     |     |
| Intermenstrual bleeding | 3 | 8  |     |     |

Ocular disorders

| Eye irritation | 4 | 10 |     |     |
| Blurred vision | 4 | 10 |     |     |
| Dry eye | 3 | 8  |     |     |
| Painful red eye | 2 | 5  |     |     |

Renal and urinary disorders

| Renal failure | 3 | 8 | 1 | 3 |
| Renal impairment | 3 | 8 |     |     |
| Oliguria | 2 | 5 |     |     |
| Incontinence | 2 | 5 |     |     |

Ear disorders

| Earache | 3 | 8 |     |     |
| Tinnitus | 2 | 5 |     |     |

Other Clinically Relevant Adverse Reactions

Leukocytosis

TRISENOX can induce proliferation of leukemic promyelocytes resulting in a rapid increase in white blood cell count. Leukocytosis greater than 10 G/l developed during induction therapy in 43% patients receiving TRISENOX/tretinoin for newly-diagnosed low-risk APL and in 50% of patients receiving TRISENOX monotherapy for relapsed/refractory APL. In the relapsed/refractory setting, a relationship did not exist between baseline WBC counts and development of hyperleukocytosis nor baseline WBC counts and peak WBC counts.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of TRISENOX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Cardiac disorders: Ventricular extrasystoles in association with QT prolongation, ventricular tachycardia in association with QT prolongation, including torsades de pointes, atrioventricular block, and congestive heart failure

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 (see Warnings and Precautions [5.1]). Discontinue or replace with an alternative drug that does not prolong the QT/QTc interval while the 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 (see Warnings and Precautions [5.1]). Avoid concomitant use 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

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 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. These findings occurred in mice administered a 10 mg/kg dose of a 5 times the projected human dose on a mg/m² basis. In hamsters, 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% to 4% and 15% to 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 derrhagic 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 prawns 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 arsenic trioxide on gestation day 9 (approximately 10 times the recommended human daily dose on a mg/m² basis). 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.

8.2 Lactation

Risk Summary

Arsenic trioxide is excreted in human milk. There are no data 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, advise women not to breastfeed during treatment with TRISENOX and for 2 weeks after the final dose.

8.3 Females and Males of Reproductive Potential

TRISENOX can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations [8.1]).

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with TRISENOX and for 6 months after the final dose.
TRISENOX® (arsenic trioxide) injection

Males
Advises males with female partners of reproductive potential to use effective contraception during treatment with TRISENOX and for 3 months after the final dose.

Infertility
Males
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 (13.3)].

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 pharmacokinetic data in pediatric patients with APL treated with TRISENOX 0.15 mg/kg/day. The pharmacokinetics of arsenic trioxide in pediatric patients with APL were evaluated following administration of 0.25 to 0.50 mg/kg of arsenic trioxide in patients with APL. The pharmacokinetics of AsIII, AsV, and the pentavalent metabolites MMAV and DMAV were evaluated in pediatric patients with APL. The mean AUCiv for AsIII was comparable among the normal, mild and moderate renal impairment groups. However, the severe renal impairment group had a 2-fold increase in the AUCiv for AsIII. The methylated metabolites of AsIII, MMAV, DMAV, are primarily excreted in the urine. The total clearance of AsIII 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 to 32 mg.

10 OVERDOSE

10.1 Overdose Manifestations

Overdose of arsenic trioxide may be higher in patients with severe renal impairment [see Clinical Pharmacology (12.3)]. The use of TRISENOX in patients with severe hepatic impairment (Child-Pugh Class C) has not been studied.

10.2 Excretion

The effect of renal impairment on the pharmacokinetics of AsIII, AsV, and the pentavalent metabolites MMAV and DMAV was evaluated in patients with advanced malignancies who were classified as having normal renal function (creatinine clearance [Clcr] > 80 mL/min, n=6), mild renal impairment (Clcr 50 to 80 mL/min, n=5), moderate renal impairment (Clcr 30 to 49 mL/min, n=8), or severe renal impairment (Clcr < 30 mL/min, n=8). The total plasma clearance of AsIII 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 to 32 mg.

Specific Populations

10.2.1 Patients with Renal Impairment

The effect of renal impairment on the pharmacokinetics of AsIII, AsV, and the pentavalent metabolites MMAV and DMAV was evaluated in patients with advanced malignancies who were classified as having normal renal function (creatinine clearance [Clcr] > 80 mL/min, n=6), mild renal impairment (Clcr 50 to 80 mL/min, n=5), moderate renal impairment (Clcr 30 to 49 mL/min, n=8), or severe renal impairment (Clcr < 30 mL/min, n=8). The total plasma clearance of AsIII 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 to 32 mg.

Specific Populations

10.2.2 Patients with Hepatic Impairment

The effect of hepatocellular injury on the pharmacokinetics of AsIII, AsV, and the pentavalent metabolites MMAV and DMAV was evaluated in patients with advanced malignancies who 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=5) or severe hepatic impairment (Child-Pugh class C, n=9). The effect of hepatic injury on the pharmacokinetics of MMAV and DMAV was evaluated in patients with severe hepatic impairment (Clcr < 30 mL/min, n=8). The mean AUCiv for AsIII was comparable among the normal, mild and moderate renal impairment groups. However, the severe renal impairment group had a 2-fold increase in the AUCiv for AsIII. MMAV and DMAV were reduced in the group with severe renal impairment, whereas in the severe hepatically impaired patient, MMAV and DMAV were reduced. The effect of hepatic injury on the pharmacokinetics of MMAV and DMAV was evaluated in patients with severe hepatic impairment (Clcr < 30 mL/min, n=8). The mean AUCiv for AsIII was comparable among the normal, mild and moderate renal impairment groups. However, the severe renal impairment group had a 2-fold increase in the AUCiv for AsIII. MMAV and DMAV were reduced in the group with severe renal impairment, whereas in the severe hepatically impaired patient, MMAV and DMAV were reduced. The effect of hepatic injury on the pharmacokinetics of MMAV and DMAV was evaluated in patients with severe hepatic impairment (Clcr < 30 mL/min, n=8). The mean AUCiv for AsIII was comparable among the normal, mild and moderate renal impairment groups. However, the severe renal impairment group had a 2-fold increase in the AUCiv for AsIII. MMAV and DMAV were reduced in the group with severe renal impairment, whereas in the severe hepatically impaired patient, MMAV and DMAV were reduced.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with TRISENOX [see Warnings and Precautions (5.6)].

12.3 Pharmacokinetics

The inorganic, polyphosphinated form of arsenic trioxide, when placed into solution, immediately forms the hydrolys product arsenic acid (AsIII). AsIII is the pharmacologically active species of arsenic trioxide. Monomethylarsonic acid (MMAV) and dimethylarsinic acid (DMAV) are the main pentavalent metabolites formed during metabolism, in addition to arsenic acid (AsIII) as a product of AsIII oxidation. The pharmacokinetics of arsenic species [AsIII, MMAV, DMAV] 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 arsenic acid (AsIII), the primary active arsenic species were reached at the end of infusion (2 hours). Plasma concentration of AsIII 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 AsIII (mean AUCiv,0-INF) was 194 ng·h/mL (n=5) on Day 1 of Cycle 1 and 332 ng·h/mL (n=6) on Day 25 of Cycle 2, which represents an approximate 2-fold accumulation. The primary pentavalent metabolites, MMAV and DMAV, are slow to appear in plasma (approximately 10 to 24 hours after first administration of arsenic trioxide), but, due to their longer half-life, accumulate more upon multiple dosing than does AsIII. The mean estimated terminal elimination half-lives of the metabolites MMAV and DMAV are 32 hours and 72 hours, respectively. Metabolism

Much of the AsIII is distributed to the tissues where it is methylated to the less cytotoxic metabolites, monomethylarsonic acid (MMAV) and dimethylarsinic acid (DMAV) by methyltransferases primarily in the liver. The metabolism of arsenic trioxide also involves oxidation of AsIII to AsV, which may occur in numerous tissues via enzymatic or nonenzymatic processes. AsV is present in plasma only at relatively low levels.

Distribution

The volume of distribution (Vss) for AsIII is large (mean 562 L, n=10) indicating that AsIII is widely distributed throughout body tissues. Vss is also dependent on body weight and increases as body weight increases.

Elimination

Metabolism

Much of the AsIII is distributed to the tissues where it is methylated to the less cytotoxic metabolites, monomethylarsonic acid (MMAV) and dimethylarsinic acid (DMAV) by methyltransferases primarily in the liver. The metabolism of arsenic trioxide also involves oxidation of AsIII to AsV, which may occur in numerous tissues via enzymatic or nonenzymatic processes. AsV 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 AsIII. The methylated metabolites of AsIII, MMAV, DMAV, are primarily excreted in the urine. The total clearance of AsIII 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 to 32 mg.

Specific Populations

13.1.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with TRISENOX [see Warnings and Precautions (5.6)].
Arsenic trioxide and trivalent arsenite salts have not been demonstrated to be mutagenic to bacteria, yeast, or mammalian cells. Arsenite salts are clastogenic in vitro (human fibroblast, human lymphocytes, Chinese hamster ovary cells, Chinese hamster V79 lung cells). Trivalent arsenic was genotoxic in the chromosome aberrations assay and micronucleus bone marrow assay in mice. The effect of arsenic on fertility has not been adequately studied in humans. Decreased testicular weight and impaired spermatogenesis have been reported in animal studies. Male Wistar rat pups were administered 15 mg/kg sodium arsenite solution via the intraperitoneal route from postnatal days 1 to 14 and testes were collected for evaluation on postnatal days 15, 21, and 50. Results of this study revealed an altered morphology of the seminiferous tubules along with degeneration of spermatogenic cells, increased number of sperm with abnormal morphology, and decreased sperm counts. In beagle dogs administered intravenous arsenic trioxide for 90 days, reduced inner cell layers within seminiferous tubules and significantly decreased numbers of spermatocytes, spermatids, and sperm were observed at doses of 1 mg/kg/day and higher. The 1 mg/kg/day dose is approximately 3 times the recommended human daily dose on a mg/m² basis.

**CLINICAL STUDIES**

### 14.1 Newly-Diagnosed 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 Gi/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 hematologic complete remission (CR) or for a maximum of 60 days. Patients in this group who achieved a CR during induction received 4-8 week cycles of consolidation treatment with TRISENOX 0.15 mg/kg intravenously once daily for 5 days every week during weeks 1 to 4 of the 8-week cycle, in combination with tretinoin 22.5 mg/m² (rounded to the nearest 10 mg increment) orally twice daily during weeks 1 to 2 and 5 to 6 of the 8-week cycle. TRISENOX was omitted during weeks 5 to 6 of the last cycle.

Patients in the chemotherapy/tretinoin group received idarubicin 12 mg/m² intravenously once daily on days 1-4, 2-4, 6, and 8 in combination with tretinoin 22.5 mg/m² (rounded to the nearest 10 mg increment) orally twice daily, starting on day 1, until hematologic CR or for a maximum of 60 days. Patients in this group who achieved a CR during induction received consolidation and maintenance treatment with tretinoin in combination with chemotherapy.

The trial enrolled 162 patients with a morphologic diagnosis of APL. The median age of patients was 45 years in the TRISENOX/tretinoin arm and 47 years in the chemotherapy/tretinoin arm, and 52% and 46% were male in the TRISENOX/tretinoin and chemotherapy/tretinoin arms, respectively. Baseline characteristics were balanced between treatment arms, including median WBC count, platelet count, PML-RARA isoform, and FLT3-ITD status.

Efficacy was based on event-free survival (EFS) rate at 2 years. EFS was defined as the time from randomization to the occurrence of treatment failure, defined as neither achievement of CR or CRi after induction therapy, no achievement of molecular remission after 3 consolidation courses, molecular relapse, hematologic relapse, or death. The primary analysis of EFS was based on the difference between the two treatment arms in patients achieving EFS at 2 years. With a median follow-up of 34.4 months, the 2-year EFS rate of the modified ITT (mITT) population (patients who received at least one dose of the assigned treatment) was 94% in the TRISENOX/tretinoin arm (n=77) versus 82% in the chemotherapy/tretinoin arm (n=79), a treatment difference of 12% (95% CI: 1.22, p-value 0.048). Overall survival (OS) for the mITT population was 95% (95% CI: 93, 100) in the TRISENOX/tretinoin arm versus 91% (95% CI: 86, 97) in the chemotherapy/tretinoin arm. The difference in 2-year OS rate between the arms was 6% (95% CI: 0, 10).

**Figure 1:** Event-Free Survival for Newly-Diagnosed APL

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months Diagnosed</th>
<th>Probability of Event-Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATRA–arsenic trioxide</td>
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<td>1.00</td>
</tr>
<tr>
<td>ATRA–chemotherapy</td>
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</tr>
<tr>
<td>ATRA–arsenic trioxide</td>
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<tr>
<td>ATRA–chemotherapy</td>
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<td>0.75</td>
</tr>
<tr>
<td>ATRA–arsenic trioxide</td>
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<td>ATRA–chemotherapy</td>
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<tr>
<td>ATRA–chemotherapy</td>
<td>1.00</td>
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The number of patients in the plot is based on the mITT population.

### 14.2 Relapsed or Refractory APL

TRISENOX was investigated in Study PLRXAS01, an open-label, single-arm trial in 40 patients with relapsed or refractory APL who were previously treated with an anthracycline and a retinoid and had relapsed or refractory APL. Patients received TRISENOX 0.15 mg/kg/day intravenously over 1 to 2 hours until the bone marrow was cleared of leukemic cells or for a maximum of 60 days. The CR (absence of visible leukemic cells in bone marrow and peripheral recovery of platelets and white blood cells with a confirmatory bone marrow ≥ 30 days later) rate in this population of previously treated patients was 28 of 40 (70%) among the 22 patients who had relapsed less than one year after treatment with tretinoin, there were 18 complete responders (82%). Of the 18 patients receiving TRISENOX ≥ 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). Cyogenetic conversion to no detection of the APL chromosome rearrangement was observed in 24 of 28 (86%) patients who met the response criteria defined above, in 5 of 5 (100%) patients who met some, but not all, of the response criteria, and 3 of 7 (43%) of patients who did not respond. RT-PCR conversions to no detection of the APL gene rearrangement were demonstrated in 22 of 28 (79%) of patients who met the response criteria, in 3 of 5 (60%) of patients who met some, but not all, of the response criteria, and in 2 of 7 (29%) of patients who did not respond.

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

### 15. REFERENCES


### 16. HOW SUPPLIED/STORAGE AND HANDLING

#### How Supplied

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

NDC 63459-600-06: 12 mg/6 mL (2 mg/mL) vial in packages of ten vials.

#### Storage and Handling

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

### 17. PATIENT COUNSELING INFORMATION

#### Differential 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 [see Warnings and Precautions (5.3)].

#### Cardiovascular Abnormalities

Advise patients that TRISENOX may cause ECG abnormalities, including QT prolongation. 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 [see Warnings and Precautions (5.2) and Drug Interactions (7)].

#### Encephalopathy and Wernicke's Encephalopathy (WE)

Advise patients that symptoms of encephalopathies include neurological symptoms such as confusion, decreased level of consciousness, seizures, cognitive deficits, ataxia, visual symptoms and oculomotor dysfunction. Advise patients and caregivers to closely monitor for neurological symptoms and immediately report them to their healthcare provider [see Warnings and Precautions (5.3)].

#### Thromboembolism

Advise males with female partners of reproductive potential to use effective contraception during treatment with TRISENOX and for 6 months after the last dose [see Use in Specific Populations (8.3)].

#### Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.5) and Use in Specific Populations (8.1)].

#### Other Adverse Reactions

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. Advise patients to call their healthcare provider at the onset of any adverse reactions [see Adverse Reactions (6.1)].

### 18. MANUFACTURED FOR:

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Parsippany, NJ 07054

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