ARSENIC TRIOXIDE- arsenic trioxide injection

FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE
Arsenic trioxide injection is an arsenical 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.

- For consolidation, the recommended dose of arsenic trioxide injection is 0.15 mg/kg intravenously daily for 25 doses over a period up to 5 weeks. Begin consolidation 3 to 6 weeks after completing induction therapy.

- For the consolidation cycle, the recommended dose of arsenic trioxide injection is 0.15 mg/kg intravenously daily until bone marrow remission. Do not exceed 60 doses for total induction.

- In patients with ventricular arrhythmia or prolonged QTcF, delay the reintroduction of arsenic trioxide injection after an interval of 6 weeks or until the QTcF interval is normalized.

- Patients treated with arsenic trioxide injection may develop differentiation syndrome, which can be fatal if not treated. Symptoms may include fever, dyspnea, acute respiratory distress, pulmonary infiltrates, pleural or pericardial effusions, weight gain or peripheral edema, hypotension, and renal, hepatic, or multi-organ dysfunction, in the presence or absence of bone marrow suppression. If differentiation syndrome is suspected, immediately discontinue arsenic trioxide injection and start high-dose corticosteroid therapy and hemodynamic monitoring until resolution of signs and symptoms. Temporary discontinuation of arsenic trioxide injection may be required before discontinuing drugs known to prolong QT interval. Do not administer arylamine or norarlyamine agents within 48 hours of arsenic trioxide injection.

WARNING: DIFFERENTIATION SYNDROME AND CARDIAC CONDUCTION ABNORMALITIES
- Differentiation Syndrome: Patients with acute promyelocytic leukemia (APL) treated with arsenic trioxide injection have experienced cases of differentiation syndrome, which can be fatal if not treated. Symptoms may include fever, dyspnea, acute respiratory distress, pulmonary infiltrates, pleural or pericardial effusions, weight gain or peripheral edema, hypotension, and renal, hepatic, or multi-organ dysfunction, in the presence or absence of bone marrow suppression. If differentiation syndrome is suspected, immediately discontinue arsenic trioxide injection and start high-dose corticosteroid therapy and hemodynamic monitoring until resolution of signs and symptoms. Temporary discontinuation of arsenic trioxide injection may be required before discontinuing drugs known to prolong QT interval. Do not administer arylamine or norarlyamine agents within 48 hours of arsenic trioxide injection.

- Cardiac Conduction Abnormalities: Arsenic trioxide injection can cause QT interval prolongation, complete atrioventricular block, and a torsade de pointes-type ventricular arrhythmia, which can be fatal. Before initiating therapy, assess the QTcF interval, correct pre-existing electrolyte imbalances, and consider discontinuing drugs known to prolong QTF interval. Do not administer arylamine or norarlyamine agents within 48 hours of arsenic trioxide injection.

ADVERSE REACTIONS
- The most common adverse reactions (greater than 30%) were leukocytosis, neutropenia, thrombocytopenia, nausea, vomiting, anemia, edema, hypotension, and renal, hepatic, or multi-organ dysfunction.

- Potentially life-threatening adverse reactions that may require dose interruption, dose reduction, or permanent discontinuation of arsenic trioxide injection are:

- Differentiation syndrome
- Congestive heart failure
- Torsade de pointes-type ventricular arrhythmia
- QT prolongation

DOSAGE AND ADMINISTRATION

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage
- Arsenic trioxide injection is administered intravenously daily for 25 doses over a period up to 5 weeks. Begin consolidation 3 to 6 weeks after completing induction therapy.

2.2 Dose Modifications for Toxicities
- For leukocytosis, neutropenia, or thrombocytopenia, dose reduction may be warranted.
- For renal impairment, monitor patients with severe renal impairment (creatinine clearance less than 30 mL/min) for adverse reactions when treated with arsenic trioxide injection.
- For differentiation syndrome, immediately initiate high-dose corticosteroid therapy and hemodynamic monitoring until resolution of signs and symptoms. Temporary discontinuation of arsenic trioxide injection may be required before discontinuing drugs known to prolong QT interval. Do not administer arylamine or norarlyamine agents within 48 hours of arsenic trioxide injection.

8 CLINICAL STUDIES

8.1 Induction Therapy
- Patients treated with arsenic trioxide injection to patients with ventricular arrhythmia or prolonged QTcF. Do not administer arylamine or norarlyamine agents within 48 hours of arsenic trioxide injection.

8.2 Lactation
- Advise women not to breastfeed. (3)
Safety information was available for 52 patients with relapsed or refractory APL who participated in Relapsed or Refractory APL and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience

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

6 ADVERSE REACTIONS

8.1 Differentiation Syndrome

Differentiation syndrome, which may be life-threatening or fatal, has been observed in patients with acute promyelocytic leukemia (APL) treated with arsenic trioxide injection (technical trials). Up to 25% of patients treated with arsenic trioxide injection in APL developed differentiation syndrome. Symptoms of differentiation syndrome include fever, chills, dyspnea, pericardial pain, hypoxemia, weight gain, peripheral edema, hypotension, renal failure, hepatotoxicity, neurologic abnormalities, respiratory failure, hemodynamic instability, multi-organ failure, disseminated intravascular coagulation, respiratory failure, and death. In clinical trials of patients with relapsed or refractory APL treated with arsenic trioxide injection, 16-23% of patients treated with arsenic trioxide injection for APL developed differentiation syndrome. Symptoms have abated for at least 3 days after discontinuation of arsenic trioxide injection infusion, and it usually resolved by 8 weeks after arsenic trioxide injection infusion. There are no data on the effect of arsenic trioxide injection on the QTc interval during the infusion of the drug. Arsenic trioxide injection monotherapy, 40% had at least one ECG tracing with a QTc interval greater than 470 ms.

5 WARNINGS AND PRECAUTIONS

A related trivalent arsenic, arsenic trioxide injection is contraindicated in patients who are hypersensitive to arsenic.

3.2.3 Instructions for Preparation and Intravenous Administration

Reconstitution

Dilute arsenic trioxide injection 100 to 250 mL 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP, using proper aseptic technique, immediately after withdrawal from vial. Do not store reconstituted solutions for more than 24 hours at room temperature or 40°C (104°F).

Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Administer arsenic trioxide injection intravenously over 2 hours. The infusion duration may be extended up to 3 hours if arterial needle reaction is observed. A median infusion rate is recommended.

The arsenic trioxide injection is infused in a single dose and does not require protection. Unused portions of each vial should be discarded properly. Do not mix arsenic trioxide injection with other medications.

Subcutaneous injection

Dosage and Administration (2.2)

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The arsenic trioxide injection is infused in a single dose and does not require protection. Unused portions of each vial should be discarded properly. Do not mix arsenic trioxide injection with other medications.
clinical trial of arsenic trioxide injection: Forty patients in the Phase 2 study received the recommended dose. A total of 12 patients had a relapsed APL, and evaluation of the impact of arsenic trioxide on these patients was performed. Adequate data are available for the 9 patients who received arsenic trioxide for relapsed APL. Arsenic trioxide was given daily for up to 28 days, except for 3 patients who received additional 21-day treatment cycles. All patients had a relapsed APL at the start of this trial, and all 12 patients were previously treated with conventional chemotherapy and/or hypoglycemia. The most common adverse events were normocytic normochromic anemia, leukocytosis, gastrointestinal symptoms, and neuropsychiatric disorders. Most patients experienced some degree of toxicity, most commonly leukocytosis, gastrointestinal symptoms, and psychiatric symptoms. Arsenic trioxide was generally well tolerated in this trial.

Table 1: Adverse Reactions in ≥5% of Patients Treated with Arsenic Trioxide Injection

<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>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>25 (63)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Fever</td>
<td>25 (63)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Bacterial infection - non-specific</td>
<td>16 (40)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>16 (40)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>16 (40)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Cough</td>
<td>16 (40)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>16 (40)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>16 (40)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Headache</td>
<td>16 (40)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16 (40)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Nervous disorders</td>
<td>16 (40)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>16 (40)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Cardiovascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG/QC corrected interval prolong</td>
<td>16 (40)</td>
<td>2 (5)</td>
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<tr>
<td>ECG abnormal other than QT interval prolong</td>
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<tr>
<td>Metabolic and nutrition disorders</td>
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<tr>
<td>Hyperglycemia</td>
<td>20 (50)</td>
<td>5 (13)</td>
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<td>3 (8)</td>
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<tr>
<td>Hypokalemia</td>
<td>10 (25)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>AST increased</td>
<td>10 (25)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10 (25)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>5 (13)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>5 (13)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>3 (8)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>3 (8)</td>
<td>1 (3)</td>
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<tr>
<td>Neutropenia</td>
<td>3 (8)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>3 (8)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis</td>
<td>17 (43)</td>
<td>1 (3)</td>
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<tr>
<td>Blister</td>
<td>3 (8)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Infection</td>
<td>3 (8)</td>
<td>1 (3)</td>
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<tr>
<td>Vascular disorders</td>
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<td></td>
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<td>Hypertension</td>
<td>10 (25)</td>
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<tr>
<td>Hepatic</td>
<td>10 (25)</td>
<td>2 (5)</td>
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<tr>
<td>Neutropenia</td>
<td>7 (17)</td>
<td>1 (3)</td>
</tr>
<tr>
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<td>6 (15)</td>
<td>1 (3)</td>
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<tr>
<td>Neutropenia</td>
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<td>1 (3)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4 (10)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

| Reproductive system disorders      |                             |                           |
| Reproduction                       | 2 (5)                       | 1 (3)                     |
| Neutropenia                        | 2 (5)                       | 1 (3)                     |
| Neutropenia                        | 1 (3)                       |                           |
8.6 Patients with Renal Impairment

In efficacy and safety were observed by age.

8.5 Geriatric Use

The safety and efficacy of arsenic trioxide injection as a single agent in older patients with relapsed or

8.4 Pediatric Use

potential observed in animal studies, arsenic trioxide injection may impair fertility in males of reproductive

8.3 Females and Males of Reproductive Potential

arsenic trioxide injection and for six months after the final dose.

8.2 Lactation

Arsenic trioxide injection may warrant treatment with hydroxyurea (see Dosage and Administration [2.2]).

8.1 Pregnancy

8 USE IN SPECIFIC POPULATIONS

Human Data

One patient was reported to deliver a live infant with no reported congenital anomalies after receiving

Risk Summary

Based on testicular toxicities including decreased testicular weight and impaired spermatogenesis, has been reported with the use of arsenic trioxide injection for the treatment of malignancies other than APL (see Basing Basing). Infections and Infections: Hepatitis acute.

Investigation: Gamma-glutamyltransferase increased

Malignant and or lymphoma: Bone pain, myalgia, myeloproliferative

Reproductive, skin, and systemic disorders: Differentiation syndrome, acute respiratory distress syndrome, has been reported with the use of arsenic trioxide injection for the treatment of malignancies other than APL (see Basing Basing). Ear and labyrinth disorders: Deafness

Nephrogenic fibrosis, malignant and or lymphoid: Bladder, prostate, cancer, oesophageal cell carcinoma

Skin and connective tissue disorders: Localised epidermal necrolysis.

7 DRUG INTERACTIONS

Drug-Drug Interactions (7.1)

Concurrent use of these drugs and arsenic trioxide injection may increase the risk of serious QT/QTc

interval prolongation. Coadminister or replace with an alternative drug that does not prolong the QT/QTc

interval while patient is using arsenic trioxide injection. Monitor ECGs more frequently in patients when

it is not feasible to avoid concomitant use.

Drug-Drug Interactions (7.1)

Concurrent use of these drugs and arsenic trioxide injection, particularly when dose is increased in

concomitant administration of drugs that have a low incidence in electrolyte abnormalities. Monitor electrolytes

more frequently in patients when it is not feasible to avoid concomitant use of these drugs and arsenic trioxide

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more frequently in patients when it is not feasible to avoid concomitant use.
Exposure of arsenical trioxide may be higher in patients with severe renal impairment (see Clinical Pharmacology (12.2)). Patients with severe renal impairment (creatinine clearance < 30 mL/min) should undergo dietary restrictions when these patients are treated with arsenical trioxide, and a dose reduction may be necessary.

The use of arsenical trioxide injection in patients on dialysis has not been evaluated.

8.7 Patients with Hepatic Impairment

Since limited data are available on all hepatic impairment groups, caution is advised in the use of arsenical trioxide injection in patients with hepatic impairment (see Clinical Pharmacology (12.2)). Monitor patients with hepatic impairment (Child-Pugh Class C) who are treated with arsenical trioxide injection for toxicity.

10. OVERDOSAGE

10.1 Manifestations

Manifestations of arsenical trioxide injection overdose include convulsions, muscle weakness, and confusion.

10.2 Management

The injectable solution of arsenical trioxide is not expected to cause serious organ system toxicity. Treatment of an arsenical trioxide injection overdose is primarily supportive and symptomatic. If an overdose is suspected, contact a poison control center or emergency room immediately. Arsenical trioxide injection is a sterile injectable solution of arsenic trioxide. The molecular formula of the drug substance is As2O3, with a molecular weight of 197.8 atomic mass units. The following structural formula can be used to understand the chemical composition of arsenical trioxide injection:

\[
\text{ArSbCl}_3 = \text{As}_2\text{Sb}_2\text{Cl}_6
\]

Arsenic trioxide injection is available in 10 mL single-dose vials containing 10 mg of arsenic trioxide. Arsenical trioxide injection is formulated as a sterile, isosmotic, pyrogen-free solution of arsenic trioxide in water for injection using sodium chloride and diatomaceous earth as a pH-adjusting agent. Arsenical trioxide injection is a sterile injectable solution of arsenic trioxide. The molecular formula of the drug substance is As2O3, with a molecular weight of 197.8 atomic mass units. The following structural formula can be used to understand the chemical composition of arsenical trioxide injection:

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12. CLINICAL PHARMACOLOGY

12.2 Mechanism of Action

The mechanism of action of arsenical trioxide injection is not completely understood. Arsenical trioxide causes morphological changes and DNA fragmentation characteristics of apoptosis in vitro and in vivo. This results in the induction of the Fas system, proapoptotic Bcl-2 family (Bak, Bax), and cytochrome C (Cytc) with subsequent activation of the caspase cascade. The Fas receptor pathway is mediated by Fas ligand (FasL). FasL is expressed on numerous cells via enzymatic or nonenzymatic processes. As such, persistent Fas engagement is characterized by an initial rapid distribution phase and a terminal elimination half-life of approximately 500 msec. Prolongation of the QTc interval greater than 10% was comparable among the normal, mild, and moderate renal impairment groups. However, in the severe renal impairment group, the mean AUC0-24 for As[III] was 48% higher than that in the normal group. The time to steady-state plasma levels was generally below the limit of quantification injection of well tolerated renal function loss in specific populations (6.4). The use of arsenical trioxide injection in patients on dialysis has not been evaluated.

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Arsenic trioxide has been investigated in study PLRXASC, an open-label, single-centre trial in 48 relapsed or refractory APL patients, previously treated with all available agents and novel regimens. Patients received intravenous arsenic trioxide injection for 25 days at an initial dose of 5 mg/m² per day (rounded up to 10 mg/m²) and were then instructed to receive 1 to 3 additional 25-day courses of arsenic trioxide injection at the same dose, each 25 additional days over a period up to 5 weeks. In follow-up treatment, 10 patients received further arsenic trioxide injection as a maintenance course. Follow-up occurred for a mean of 27 months (range 4–60 months). Among the 100 patients who met the response criteria, 61 (61%) patients achieved complete remission (CR). Of the 39 patients receiving arsenic trioxide injection and who met the response criteria, 61 (61%) patients achieved CR. No patients had a relapse within 5 years of arsenic trioxide injection therapy. Among the 39 patients, 66% (26/39) achieved a molecular response, defined as no detectable APL RNA in the blood and bone marrow, with a median follow-up period of 17 months (range 4–60 months). These patients were not exposed to any other drugs that could have contributed to these responses. The results of this study showed that arsenic trioxide injection therapy is an effective treatment for APL patients who have been treated with previous conventional chemotherapy regimens. However, the study had several limitations, including its open-label design, small sample size, and lack of a control group. These factors may have affected the interpretation of the results. The study also lacked data on the long-term effects of arsenic trioxide injection therapy on patient outcomes. Therefore, further research is needed to determine the efficacy and safety of arsenic trioxide injection as a treatment for APL patients.
ARSENIC TRIOXIDE
arsenic trioxide injection

Product Information

Product Type: HUMAN PRESCRIPTION DRUG
Item Code (Source): NDC:50742-438

Route of Administration: INTRAVENOUS

Active Ingredient/Active Moiety

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<thead>
<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARSENIC TRIOXIDE</td>
<td>ARSENIC CATION (3+)</td>
<td>1 mg in 1 mL</td>
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Inactive Ingredients

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<thead>
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<th>Ingredient Name</th>
<th>Strength</th>
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<tr>
<td>SODIUM HYDROXIDE</td>
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<tr>
<td>HYDROCHLORIC ACID</td>
<td>(UNII: QTT17582CB)</td>
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Packaging

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<td>1</td>
<td>NDC:50742-438-10</td>
<td>1 mL in 1 CARTON</td>
<td>11/15/2018</td>
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<td>2</td>
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<td>10 mL in 1 VIAL, GLASS; Type 0: Not a Combination</td>
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Marketing Information

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</table>

Labeler - Ingenus Pharmaceuticals, LLC (833250017)
Registrant - Ingenus Pharmaceuticals, LLC (833250017)
Establishment

Ingenus Pharmaceuticals
GmbH
482730327
analysis(50742-438), label(50742-438), manufacture(50742-438), pack(50742-438), sterilize(50742-438)

Revised: 11/2018