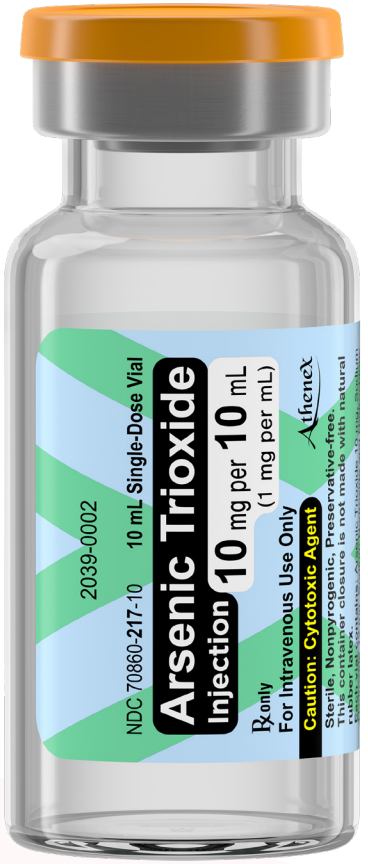
Arsenic Trioxide

Injection

10 mg per 10 mL | NDC 70860-217-10



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PLEASE SEE FULL PRESCRIBING INFORMATION, INCLUDING BOXED WARNING, FOR ARSENIC TRIOXIDE INJECTION, ENCLOSED.

THE NEXT GENERATION OF PHARMACY INNOVATION

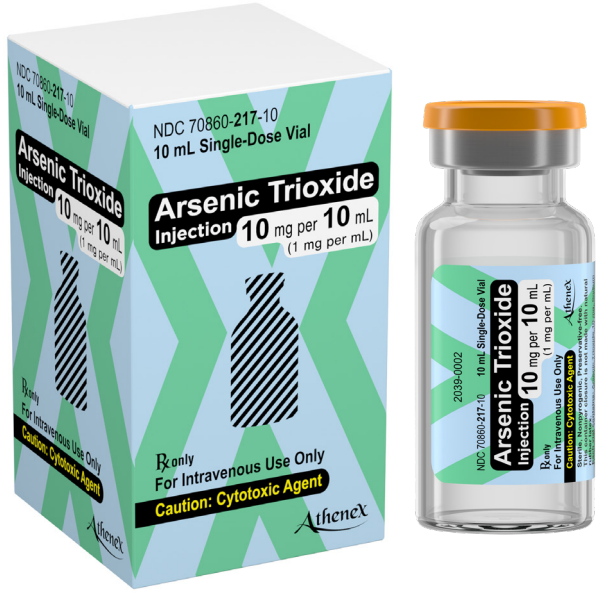
Arsenic Trioxide

Injection

10 mg

NDC 70860-217-10
10 mg per 10 mL

DESCRIPTION	Single-Dose Vial
CONCENTRATION	1 mg per mL
CLOSURE	20 mm
UNIT OF SALE	1 vial
BAR CODED	Yes
STORAGE	Room Temperature



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ARSENIC TRIOXIDE Injection

INDICATION AND USAGE

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

IMPORTANT SAFETY INFORMATION

WARNING: DIFFERENTIATION SYNDROME, CARDIAC CONDUCTION ABNORMALITIES AND ENCEPHALOPATHY INCLUDING WERNICKE'S

Differentiation Syndrome: Patients with acute promyelocytic leukemia (APL) treated with arsenic trioxide injection have experienced differentiation syndrome, which may be life-threatening or fatal. Signs and symptoms may include unexplained fever, dyspnea, hypoxia, acute respiratory distress, pulmonary infiltrates, pleural or pericardial effusions, weight gain, peripheral edema, hypotension, renal insufficiency, hepatopathy, and multi-organ dysfunction, in the presence or absence of leukocytosis. If differentiation syndrome is suspected, immediately initiate high-dose corticosteroids and hemodynamic monitoring until resolution. Temporarily withhold arsenic trioxide injection.

Cardiac Conduction Abnormalities: Arsenic trioxide injection can cause QTc interval prolongation, complete atrioventricular block and torsade de pointes, which can be fatal. Before administering arsenic trioxide injection, assess the QTc interval, correct electrolyte abnormalities, and consider discontinuing drugs known to prolong QTc interval. Do not administer arsenic trioxide injection to patients with a ventricular arrhythmia or prolonged QTc interval. Withhold arsenic trioxide injection until resolution and resume at reduced dose for QTc prolongation.

Encephalopathy: Serious encephalopathy, including Wernicke's, has occurred with arsenic trioxide injection. Wernicke's is a neurologic emergency. Consider testing thiamine levels in patients at risk for thiamine deficiency. Administer parenteral thiamine in patients with or at risk for thiamine deficiency. Monitor patients for neurological symptoms and nutritional status while receiving arsenic trioxide injection. If Wernicke's encephalopathy is suspected, immediately interrupt arsenic trioxide injection and initiate parenteral thiamine. Monitor until symptoms resolve or improve and thiamine levels normalize.

CONTRAINDICATIONS

- Arsenic trioxide injection is contraindicated in patients with hypersensitivity to arsenic.

WARNINGS and PRECAUTIONS

- **Differentiation Syndrome.** Differentiation syndrome, which may be life-threatening or fatal, has been observed in patients with APL treated with arsenic trioxide injection. In clinical trials, 16 to 23% of patients treated with arsenic trioxide injection 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 without concomitant leukocytosis, and it has occurred as early as day 1 of induction to as late as the second month induction therapy. If differentiation syndrome is suspected, temporarily withhold arsenic trioxide injection 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.

- **Cardiac Conduction Abnormalities.** Patients treated with arsenic trioxide injection can develop QTc prolongation, torsade de pointes, and complete atrioventricular block. In the clinical trials of patients with relapsed or refractory APL treated with arsenic trioxide injection 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 arsenic trioxide injection infusion, and it usually resolved by 8 weeks after arsenic trioxide injectioninfusion. There are no data on the effect of arsenic trioxide injection on the QTc interval during the infusion of the drug.

  The risk of torsade de pointes 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 arsenic trioxide injection is coadministered with medications that can lead to electrolyte abnormalities (such as diuretics or amphotericin B).

  Prior to initiating therapy with arsenic trioxide injection, assess the QTc interval by electrocardiogram, correct pre-existing electrolyte abnormalities, and consider discontinuing drugs known to prolong QTc interval. Do not administer arsenic trioxide injection 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. During arsenic trioxide injection therapy, maintain potassium concentrations above 4 mEq/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 arsenic trioxide injection and any medication known to prolong the QTc interval. Correct electrolyte abnormalities. When the QTc normalizes and electrolyte abnormalities are corrected, resume arsenic trioxide injection at a reduced dose.

- **Encephalopathy.** Serious encephalopathies were reported in patients receiving arsenic trioxide injection. 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. Wernicke's Encephalopathy Wernicke's encephalopathy occurred in patients receiving arsenic trioxide injection. 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 arsenic trioxide injection. If Wernicke's encephalopathy is suspected, immediately interrupt arsenic trioxide injection

and initiate parenteral thiamine. Monitor until symptoms resolve or improve and thiamine levels normalize.

- **Hepatotoxicity.** During treatment with arsenic trioxide injection, monitor hepatic function tests at least twice weekly during induction and at least once weekly during consolidation. Withhold arsenic trioxide injection if elevations in AST or alkaline phosphatase occur to greater than 5 times the upper limit of normal and/or elevation in serum total bilirubin occurs to greater than 3 times the upper limit of normal and resume at reduced dose upon resolution.
- **Carcinogenesis.** The active ingredient of arsenic trioxide injection, arsenic trioxide, is a human carcinogen. Monitor patients for the development of second primary malignancies.
- **Embryo-Fetal Toxicity.** Arsenic trioxide injection can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with arsenic trioxide injection and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Arsenic trioxide injection and for 3 months after the last dose.

ADVERSE REACTIONS

- The most common adverse reactions (> 30%) are 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.

OVERDOSAGE

- Manifestations of arsenic trioxide injection overdosage include convulsions, muscle weakness, and confusion. For symptoms of arsenic trioxide injection overdosage, immediately discontinue arsenic trioxide injection and consider chelation therapy. A conventional protocol for acute arsenic intoxication includes dimercaprol administered at dose of 3 mg/kg intramuscularly every 4 hours until immediate life-threatening toxicity has subsided. Thereafter, penicillamine at a dose of 250 mg orally, up to a maximum frequency of four times per day (ffi 1 g per day), may be given.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch. Or call 1-800-FDA-1088.

Please see full prescribing information for ARSENIC TRIOXIDE Injection.