Arsenic Trioxide

Brand names	Trisenox
Contraindications and warnings	**U.S. boxed warning:** Arsenic trioxide has potential to cause acute promyelocytic leukemia (APL) differentiation syndrome, characterized primarily by fever, dyspnea, weight gain, pulmonary infiltrates, and pleural or pericardial effusions. High-dose steroids (dexamethasone 10 mg IV BID) should be given at the first appearance or symptoms and should be continued for at least 3 days.[1] Arsenic trioxide can cause QT prolongation resulting in torsades de pointes or complete atrioventricular block. Proper monitoring of drug therapy should include electrolytes, 12-lead ECG, creatinine, and discontinuation of other QT prolonging medications prior to administration.[1] **Contraindications:** Contraindicated in patients who are hypersensitive to arsenic.[1] **Other warnings:** Arsenic trioxide is a human carcinogen and has the potential to lead to secondary primary malignancies. Patients should be monitored accordingly for development of these malignancies.[1]
Infusion-related cautions	Arsenic trioxide should be infused IV over 1–2 hours; however, if vasomotor reactions occur, the infusion may be prolonged up to 4 hours.[1,2]
Dosage	**Consult individual protocols:** Arsenic trioxide is indicated for refractory/relapsed APL patients undergoing induction of remission or consolidation.[2-8] These patients are only able to receive arsenic trioxide if they have the t(15;17) translocation or PML/RAR-alpha gene expression.[1] It has also been shown to be of use in patients with myelodysplastic syndromes.[9,10] **Acute promyelocytic leukemia, refractory or relapsed** **Children ≥4 years of age:** One study involving 13 patients showed that arsenic trioxide 0.15 mg/kg/day had a similar toxicity profile to that of *adult* patients.[1] **Newly diagnosed acute promyelocytic leukemia** **Children 4–6 years**: 0.2 mg/kg/day (max 10 mg) daily until hematologic complete remission or a maximum of 60 doses[11] **Children >6 years:** 0.16 mg/kg/day (max 10 mg) daily until hematologic complete remission or a maximum of 60 doses[11] **Infiltrating astrocytoma** **Children ≥3 years of age:** 0.15 mg/kg/day with each fraction of radiation therapy administered[12]
Dosage adjustment in organ dysfunction	Patients with a CrCl of <30 mL/min may require a dose reduction due to increased toxicity. Arsenic trioxide should be used with caution in patients with hepatic impairment due to lack of data in this patient population.[1]
Maximum dosage	Induction dose should not exceed 60 doses of arsenic trioxide 0.15 mg/kg/day IV. Consolidation should consist of 25 doses of arsenic trioxide 0.15 mg/kg/day IV over 5 weeks.[1]
Additives	None[1]
Suitable diluents	D5W, NS, LR[1,14]
Maximum concentration	0.1 mg/mL[1]

Arsenic Trioxide

Preparation and delivery	Dilute with 100–250 mL D5W or NS immediately after withdrawal from ampule. Unused portions should be disposed of properly at time of preparation and not stored for later use.[1] Diluted solution is stable for 24 hours at room temperature and 48 hours under refrigeration.[1]
IV push	Not recommended
Intermittent infusion	Administer over 1–2 hours. May extend up to 4 hours if needed for adverse reactions. Central venous catheter is not required.[1]
Continuous infusion	Not recommended
Other routes of administration	Not recommended
Comments	**Significant adverse effects:** Arsenic trioxide is known to cause APL differentiation syndrome. Signs and symptoms consist of unexplained fever, dyspnea, weight gain, abnormal chest auscultatory findings or radiographical abnormalities. If APL differentiation syndrome is suspected, high-dose steroids should be initiated immediately and continued for 3 days or longer until symptoms are resolved.[1] Arsenic trioxide has caused cardiac conduction abnormalities such as complete heart block, QT prolongation, and torsades de pointes.[3] Assess serum electrolytes, 12-lead ECG, and creatinine prior to initiating therapy.[1] Arsenic trioxide is a known carcinogen, which has the potential to cause secondary malignancies.[14] Other adverse effects include embryo-fetal toxicity, which can cause fetal harm.[15] It is recommended that both males and females of childbearing years, undergoing therapy should use effective means of birth control.[1] Arsenic trioxide is associated with a moderate (30% to 90%) risk of emesis.[16] Antiemetic therapy should be given in order to avert any acute or delayed nausea and vomiting. The recommended therapy to prevent nausea and vomiting is a 5-HT_3 antagonist along with dexamethasone prior to chemotherapy administration.[17] It has been shown that delayed antiemetic therapy is not required with arsenic trioxide. **Monitoring:** Serum electrolytes, 12-lead ECG, and creatinine should be assessed at baseline prior to initiation of therapy. During induction, additional monitoring includes CBC, hepatic function, blood glucose, and coagulation at least twice weekly. During consolidation, weekly monitoring is recommended. **Drug interactions:** Arsenic trioxide does not participate in CYP450 metabolism. It is recommended to discontinue any QT prolonging medications prior to initiation of therapy.[1]

REFERENCES

1. Trisenox (arsenic trioxide)[prescribing information]. North Wales, PA: Teva Pharmaceuticals USA Inc; October 2015.
2. Estey E, Garcia-Manero G, Ferrajoli A, et al. Use of all-trans retinoic acid plus arsenic trioxide as an alternative to chemotherapy in untreated acute promyelocytic leukemia. *Blood*. 2006;107(9):3469-3473.
3. Fox E, Razzouk BI, Widemann BC, et al. Phase I trial and pharmacokinetic study of arsenic trioxide in children and adolescents with refractory or relapsed acute leukemia, including acute promyelocytic leukemia or lymphoma. *Blood*. 2008;111(2):566-573.
4. Gore SD, Gojo I, Sekeres MA, et al. Single cycle of arsenic trioxide-based consolidation chemotherapy spares anthracycline exposure in the primary management of acute promyelocytic leukemia. *J Clin Oncol*. 2010;28(6):1047-1053.
5. Iland HJ, Bradstock K, Supple SG, et al. All-trans-retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4). *Blood*. 2012:120(8):1570-1580.
6. Ravandi F, Estey E, Jones D, et al. Effective treatment of acute promyelocytic leukemia with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab ozogamicin. *J Clin Oncol*. 2009;27(4):504-510.
7. Shen ZX, Chen GQ, Ni JH, et al. Use of arsenic trioxide (As2O3) in the treatment of acute promyelocytic leukemia (APL): II. Clinical efficacy and pharmacokinetics in relapsed patients. *Blood*. 1997;89(9):3354-3360.
8. Tallman MS, Altman JK. How I treat acute promyelocytic leukemia. *Blood*. 2009;114(25):5126-5135.
9. Schiller GJ, Slack J, Hainsworth JD, et al. Phase II multicenter study of arsenic trioxide in patients with myelodysplastic syndromes. *J Clin Oncol*. 2006;24(16):2456-2464.