Drug Monograph

A - Drug Name

arsenic trioxide

SYNONYM(S): As_2O_3

COMMON TRADE NAME(S): Trisenox®

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B - Mechanism of Action and Pharmacokinetics

Acute promyelocytic leukemia (APL) is characterized by a reciprocal chromosomal translocations of the retinoic acid receptor alpha gene (RAR-α) on chromosome 17 and the promyelocytic leukemia gene (PML) on chromosome 15. The resulting fusion gene, PML–RAR-α , encodes a chimeric protein which causes an arrest of myeloid cell maturation at the promyelocyte stage of development.

The mechanism of action of arsenic trioxide is not completely understood but is likely multimodal. At lower doses, arsenic promoted cellular differentiations, while apoptosis was noted at higher concentrations.

Absorption	Peak plasma levels	2 hrs
	Bioavailability	Systemic exposure (AUC) appears linear at 0.15 mg/kg.
Distribution	Widely distributed throughout tissues	
	PPB	Negligible
	Distribution Sites	Liver, kidney and heart; to a lesser extent in lung, hair and nails. No evidence of distribution in adipose tissues.

	Cross blood brain barrier?	Yes
Metabolism	Methylation in the liver to less cytotoxic metabolites, monomethylarsonic acid (MMA^V) and dimethylarsinic acid (DMA^V). Oxidation of As^{III} to As^V (low plasma levels) in many tissues via enzymatic or nonenzymatic processes.	
	Active metabolites	As^{III} (primary), possibly other trivalent and pentavalent methylated metabolites
	Inactive metabolites	Yes
Elimination	Urine	15% unchanged As^{III}; 10 - 20% MMA; 60 - 70% DMA.
	Clearance	A 45% reduction in total clearance of As^{III} is noted with multiple dosing which may contribute to accumulation. Clearance is not dependent on body weight or dose administered at 0.15 mg/kg.
	Half-life	10 - 14 hours (As^{III}), 32 hours for MMA^V and 70 hours for DMA^V

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C - Indications and Status

Health Canada Approvals:

- Acute promyelocytic leukemia (APL)

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Moderate

Extravasation Potential: None

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Auditory	Ear pain (8%)	E
	Tinnitus (5%)	E
Cardiovascular	Arrhythmia (5%) (including complete AV block, sudden death)	I
	Cardiotoxicity (rare)	E D
	Hypertension (10%)	I E
	Hypotension (25%)	I E
	QT interval prolonged (33%) (3% severe)	I
	Tachycardia (55%) (mild to moderate)	I
	Venous thromboembolism (<5%)	E
Dermatological	Rash (45%) (may be severe)	E
	Skin hyperpigmentation (8%)	E
Gastrointestinal	Abdominal pain (38%)	E
	Anorexia (38%)	E
	Constipation (28%)	E
	Diarrhea (63%)	E
	Dyspepsia (10%)	I E
	Nausea, vomiting (75%)	I
General	Edema (45%) (may be severe)	E
	Fatigue (68%)	E
Hematological	Disseminated intravascular coagulation (8%)	E D
	Hyperleukocytosis	E
	Myelosuppression ± infection, bleeding (13%) (severe)	E
	Other (23%) (APL differentiation syndrome)	E
Hepatobiliary	↑ LFTs (23%) (8% severe)	E
Hypersensitivity	Hypersensitivity (5%) (3% severe)	I
Injection site	Injection site reaction (23%)	I E
Metabolic / Endocrine	Abnormal electrolyte(s) (50%) (↑/↓Mg, ↑/↓K, ↓Ca, ↓PO4; 13% severe)	E
	Hyperglycemia (45%) (severe 13%)	E

	Tumor lysis syndrome (rare)	I
Musculoskeletal	Musculoskeletal pain (33%) (severe 8%)	E
Nervous System	Anxiety (33%)	E
	Depression (20%)	E D
	Dizziness (25%)	E
	Encephalopathy (rare)	E
	Headache (63%)	E
	Insomnia (43%)	E
	Paresthesia (33%) (5% severe)	E
	Seizure (8%)	E
	Somnolence (8%)	E
Ophthalmic	Blurred vision (10%)	E
	Conjunctivitis (10%)	E
Renal	Proteinuria (5%)	E
	Renal failure (8%)	E D
Respiratory	Cough, dyspnea (65%) (severe 10%)	E
	Pneumonitis (<5%)	E
Vascular	Flushing (10%)	I E
	Vasculitis (<5%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for arsenic trioxide include nausea/vomiting, fatigue, cough/dyspnea, diarrhea, headache, tachycardia, abnormal electrolyte(s), leukocytosis, edema and hyperglycemia.

Since arsenic trioxide induces partial differentiation of APL cells, hyperleukocytosis may occur in some patients, but does not appear to be related to baseline white blood cell counts. Hyperleukocytosis usually resolved without additional chemotherapy treatment.

Life-threatening **APL differentiation syndrome** has been observed in some patients. Patients may present with dyspnea, unexplained fever, weight gain, peripheral edema, hypotension, acute renal failure, congestive heart failure and pulmonary infiltrates. Administer high-dose steroids (e.g. dexamethasone 10 mg BID) at the first signs of APL syndrome, irrespective of the leukocyte count, and continue for at least 3 days or longer until resolution. Hold arsenic trioxide treatment for patients who develop severe APL differentiation syndrome.

Most cases of **elevated transaminases** have been reported to resolve without interruption of treatment.

Although most cases of peripheral **neuropathy** are mild and moderate, some may be severe and/or irreversible.

Encephalopathy, including fatal cases, has been reported. In patients with vitamin B1 deficiency, Wernicke encephalopathy was reported after arsenic trioxide treatment. Some cases recovered with vitamin B1 supplementation.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Adults:

- Do not start treatment in patients with QT/QTc > 500 msec. Correct electrolyte abnormalities and start only if QT <430 msec for males or <450 msec for females.
- During treatment with arsenic trioxide, potassium concentration should be kept > 4 mmol/L and magnesium concentrations should be kept > 0.74 mmol/L.
- **Do not exceed the maximum number of doses recommended** for the induction and consolidation treatments.
- Obese patients should be dosed based on lean weight.

For induction treatment:

Intravenous: 0.15 mg/kg/day until bone marrow remission. Total induction dose should not exceed 60 doses.

For consolidation treatment:

Intravenous: 0.15 mg/kg/day for 25 doses over a period up to 5 weeks, starting 3 to 6 weeks after completion of induction therapy

Dosage with Toxicity:

Toxicity while on treatment	Action
QT/QTc > 500 msec	Hold; investigate and correct risk factors. May start if QTc < 430 msec for males and < 450 msec for females.
Syncope, rapid heart rate or arrhythmia	Hold. Monitor and correct electrolyte abnormalities. Restart when QT < 460 msec and syncope and arrhythmia resolve.
K ≤ 4mmol/L and/or Mg ≤ 0.74 mmol/L	Hold. Monitor and correct electrolyte abnormalities. Restart if Mg and K recover and no signs of arrhythmia.
Signs and symptoms of APL differentiation syndrome	Start high-dose steroids (e.g. dexamethasone 10mg IV BID) for ≥ 3 days until resolution of signs and symptoms. Hold arsenic trioxide for severe signs and symptoms.
Other grade 3 related non-hematological toxicity	Hold. Restart if recovered to baseline with a 50% dose reduction. If toxicity does not recur within 3 days, ↑ to previous dose. Discontinue if recurs.
Other grade 4 related non-hematological toxicity	Discontinue OR Hold. Restart if recovered to baseline with a 50% dose reduction. If toxicity does not recur within 3 days, ↑ to previous dose. Discontinue if recurs.

Overdose: Symptoms suggesting severe acute arsenic toxicity may include convulsions, muscle weakness and confusion. Discontinue drug, monitor ECG and consider chelation therapy. A suggested protocol for acute arsenic intoxication includes dimercaprol 3 mg/kg IM q4h until resolution of immediate life-threatening toxicity.

Dosage with Hepatic Impairment:

No clear increase in systemic exposure to arsenic trioxide or its metabolites with mild or moderate hepatic function was observed; dosage adjustment is likely not needed in mild to moderate liver impairment. Plasma metabolite levels may be increased in severe hepatic impairment; dose reduction should be considered in severe hepatic impairment (Child-Pugh C).

Hepatic impairment	Recommended dose
Mild (Child Pugh A)	0.15 mg/kg/day
Moderate (Child Pugh B)	0.15 mg/kg/day
Severe (Child Pugh C)	Consider decrease

Dosage with Renal Impairment:

Based on limited data, dosage adjustment is likely not needed in mild to moderate renal impairment. Dose reduction should be considered in severe renal impairment (CrCl < 30 mL/min) due to increased exposure and/or decreased clearance of metabolites. The use of arsenic trioxide in dialysis patients has not been studied.

Renal impairment	Recommended dose
Mild (CrCl 50 - 80 mL/min)	0.15 mg/kg/day
Moderate (CrCl 30 - 49 mL/min)	0.15 mg/kg/day
Severe (CrCl < 30 mL/min)	Consider decrease

Dosage in the elderly:

Limited data available; use with caution.

Dosage based on gender:

No information available.

Dosage based on ethnicity:

No information available.

Children:

There are no data for children < 5 years of age. Data is limited in pediatric patients (aged >5 to <18 years). Exposure is expected to be > 50% higher than that in adults; monitor patients closely. Obese pediatric patients should be dosed based on ideal body weight.

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F - Administration Guidelines

- Dilute dose with 100-250 mL of dextrose 5% injection or Normal Saline.
- Administer IV over 1-2 hours. The infusion duration may be extended up to 4 hours if acute vasomotor reactions are observed.
- A central venous catheter is not required.
- Do not administer in the same IV line or admix with other drugs.
- Store unopened ampoules at 15-30°C. Do not freeze.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components
- Patients with QT/QTc interval > 500 msec

Other Warnings/Precautions:

- Avoid concurrent use of drugs that prolong the QT interval or disrupt electrolyte levels. Pre-existing electrolyte abnormalities must be corrected before treatment with arsenic trioxide.
- Exercise caution in patients with increased QT interval or who are at risk (e.g. age > 65 years, low potassium/magnesium, congenital or pre-existing QT prolongation, CHF, prior anthracycline, diabetes, autonomic neuropathy).
- Exercise caution in patients with conditions that may be exacerbated by an increase in heart rate, such as tachyarrhythmias or ischemic heart disease. Patients with syncope, rapid or irregular heartbeat should be hospitalized for monitoring.
- Exercise caution in patients with renal impairment, as this may result in overdose levels of the drug and may be fatal.

- Obese patients may experience higher than expected plasma and tissue concentrations of arsenical species.
- Poor nutritional status may decrease the capacity to methylate and detoxify arsenic. Decreased glutathione levels increase arsenic concentration and toxicity.

Other Drug Properties:

- Carcinogenicity: Yes
  (observed with arsenic)

Pregnancy and Lactation:

- Embryotoxicity: Yes
  Arsenic crosses the placental barrier.
- Teratogenicity: Yes
  Arsenic trioxide is **contraindicated** in pregnancy.
  - Adequate contraception should be used by patients who can become pregnant and their partners during treatment, and for at least **6 months** after the last dose.
  - Adequate contraception should be used by patients who produce sperm and their partners during treatment, and for at least **3 months** after the last dose.
- Genotoxicity: Yes
  (weak)
- Clastogenicity: Yes
- Lactation: Contraindicated
  Arsenic is excreted in human milk; breastfeeding is **contraindicated** during treatment and for **3 months** after the last dose.
- Fertility effects: Yes

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Drugs that may prolong QT (i.e. amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol,	↑ risk of QT prolongation	Additive	Discontinue during treatment with arsenic trioxide

fluconazole, moxifloxacin, domperidone, ondansetron, etc)			
Drugs that disrupt electrolyte levels (i.e. loop/thiazide diuretics, laxatives, amphotericin B, high dose corticosteroids)	↑ risk of arrhythmias	Additive	Avoid
Previous anthracycline use	↑ risk of QT prolongation	Cardiotoxic effects	Caution
Strong Pgp or MRP inhibitors	↑ arsenic exposure and/or toxicity	↓ efflux of arsenic trioxide	Caution
CYP3A4 substrates (e.g. cyclosporine, pimozide, tacrolimus, triazolo-benzodiazepines, dihydropyridine calcium-channel blockers, certain HMG-CoA reductase inhibitors)	↓ substrate concentration and/or efficacy	↑ metabolism of CYP3A4 substrates	Caution, especially substrates with narrow therapeutic range
CYP2A substrates	↓ substrate concentration and/or efficacy	↑ metabolism of CYP2A substrates	Caution, especially substrates with narrow therapeutic range
CYP2B1/2 substrates	↓ substrate concentration and/or efficacy	↑ metabolism of CYP2B1/2 substrates	Caution, especially substrates with narrow therapeutic range

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Hospitalize patients with syncope or tachyarrhythmia.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
ECG	at baseline, twice weekly and more frequently as clinically indicated. (Consider continuous ECG monitoring for patients with risk factors for QT prolongation/torsade de pointes.)
Electrolytes (including magnesium and calcium)	At baseline and at least twice weekly, more frequently as indicated during induction; at least weekly during consolidation
Liver and renal function tests	At baseline and at least twice weekly, more frequently as indicated during induction; at least weekly during consolidation
CBC	At baseline and at least twice weekly, more frequently as indicated during induction; at least weekly during consolidation
Blood glucose levels	At baseline and at least twice weekly, more frequently as indicated during induction; at least weekly during consolidation
PT/INR	At baseline and at least twice weekly, more frequently as indicated during induction; at least weekly during consolidation
Clinical toxicity assessment for APL differential syndrome, tumour lysis syndrome, encephalopathy (especially in patients at risk of vitamin B1 deficiency), pulmonary infiltrates/effusion	Baseline and regular

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Arsenic Trioxide - First Line Consolidation of Acute Promyelocytic Leukemia (APL)
- Arsenic Trioxide - First Line Induction of Acute Promyelocytic Leukemia (APL)
- Arsenic Trioxide - Relapsed_Refractory Induction of Acute Promyelocytic Leukemia (APL)
- Arsenic Trioxide - Relapsed_Refractory Consolidation of Acute Promyelocytic Leukemia (APL)

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K - References

Prescribing Information: Trisenox (arsenic trioxide). Cephalon (US) Inc., June 2010.

Product Monograph: Trisenox® (arsenic trioxide). Teva Canada Inc., June 7, 2019.

Product Monograph: Arsenic trioxide. Sandoz Canada Inc., June 2023.

Soignet SL, Frankel SR, Douer D, et al. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. J Clin Oncol 2001;19(18):3852-60.

Soignet SL, Maslak P, Wang ZG, et al. Complete remission after treatment of acute promyelocytic leukemia with arsenic trioxide. N Engl J Med 1998;339(19):1341-8.

Summary of Product Characteristics: Trisenox (arsenic trioxide). Cephalon (UK) Ltd., January 28, 2013.

October 2023 Modified Indications and Pregnancy/lactation sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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