DRUG NAME: Arsenic trioxide

SYNONYM(S): arsenic, As_2O_3, white arsenic[1]

COMMON TRADE NAME(S): TRISENOX®

CLASSIFICATION: miscellaneous

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Arsenic is an element classed as a semi-metal or metalloid and it exists as chemically unstable oxides and sulfides as well as arsenites or arsenates of sodium, calcium, and potassium. Arsenic trioxide is an inorganic form of arsenic and is the most widely studied arsenical-based cancer drug.[1] Although its mechanism is not completely understood, arsenic trioxide may have a multi-modal mechanism of action likely dependent on dose. At lower doses, arsenic trioxide promotes partial cellular differentiation, while at higher doses it leads to morphological changes and DNA fragmentation characteristic of apoptosis. Other key effects include damage or degradation of the fusion protein PML-RARα and inhibition of growth and angiogenesis. Arsenic trioxide also reduces procoagulant activity and tissue factor gene expression. It demonstrates antivasculogenic activity in tumour xenografts and enhances the sensitivity of neoplastic cell lines and tumour xenografts to radiation therapy.[2]

PHARMACOKINETICS:

Absorption	arsenious acid (primary pharmacologically active form) formed immediately by hydrolysis in solution	
Distribution	rapid distribution to highly perfused organs; arsenic accumulates in liver, kidney, heart, and to a lesser extent in lung, hair, and nails; no evidence of distribution into adipose tissue	
	cross blood brain barrier?	yes
	volume of distribution	>400 L (arsenious acid)
	plasma protein binding	negligible
Metabolism	methylated trivalent and pentavalent metabolites of arsenious acid created principally via methylation in the liver; some oxidation via enzymatic or nonenzymatic processess	
	active metabolite(s)	arsenious acid; monomethylarsonic acid and dimethylarsinic acid (main pentavalent metabolites); arsenic acid (oxidative product)
	inactive metabolite(s)	no information found
Excretion	slow terminal elimination phase; ~2-fold accumulation of arsenious acid and up to 8-fold accumulation of pentavalent metabolites with multiple dosing	
	urine	~15% as unchanged arsenious acid; ~85% as methylated metabolites
	feces	no information found
	terminal half life	10-14 h (arsenious acid); 32 h (monomethylarsonic acid); 70 h (dimethylarsinic acid)
	clearance	49 L/h (arsenious acid); 45% reduction in total clearance of arsenious acid with multiple dosing
Children[2,3]	exposure is expected to be greater than 50% higher than in adults; terminal half-life exceeds 24 h	

Adapted from standard reference[2] unless specified otherwise.

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USES:

Primary uses:

*Leukemia, acute promyelocytic

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Contraindications:

- history of hypersensitivity reaction to arsenic trioxide
- pregnancy and nursing mothers[2]
- baseline QT/QTc interval greater than 500 msec (unless corrected and reassessed with serial ECGs)[2]

Caution:

- Arsenic trioxide can cause ***QT prolongation*** and complete atrioventricular block. Correct preexisting electrolyte disturbances prior to treatment and monitor ECG and electrolytes. Use cautiously in patients with known risk factors for torsades de pointes. Avoid concurrent therapy with other QT prolonging drugs or drugs which disrupt electrolytes as these may increase the risk of potentially fatal arrhythmias.[2]
- Arsenic trioxide can increase ***heart rate***; use caution in patients with tachyarrhythmias or ischemic heart disease or other conditions which may be exacerbated by an increase in heart rate.[2]
- ***Renal impairment*** may result in overdose levels of arsenic, which may be fatal if untreated.[2]
- ***Poor nutritional status*** may decrease the capacity to methylate and thereby detoxify arsenic trioxide.[2]

Special populations: In ***obese*** patients, dosing based on total body weight may result in higher than expected plasma and tissue concentrations. Obese pediatric patients should be dosed on ideal body weight. Monitor all obese patients closely for signs of ***acute arsenic toxicity***.[2]

Carcinogenicity: Arsenic trioxide is a known human carcinogen. Epidemiological data in humans indicates that arsenic causes cancer of the skin, bladder, kidney, liver, prostate, and lung. Methylated metabolites of arsenic trioxide may be carcinogenic following long-term exposure.[2]

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation tests. Arsenic trioxide is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[2]

Fertility: Testicular toxicities such as decreased testicular weight and impaired spermatogenesis (reduced sperm count, decreased motility, and decreased viability) have been reported in animal studies.[2]

Pregnancy: Arsenic trioxide is known to cross the placental barrier and has been shown to be embryotoxic and teratogenic in animal studies. Women are advised to avoid becoming pregnant during treatment and for 3 months after treatment cessation. Due to the possible presence of arsenic in semen of treated patients, male patients are advised to use a condom during sexual activity with a pregnant woman or woman of child-bearing potential during treatment and for 3 months after treatment cessation.[2]

Breastfeeding is not recommended during treatment and for 3 months after treatment cessation due to the excretion of arsenic in human breast milk.[2]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[4]

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Revised: 1 June 2021

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (20%, severe 5%)
	disseminated intravascular coagulation (8%, severe 8%)
	febrile neutropenia (13%, severe 8%)
	hyperleukocytosis (10-50%, severe 3%); usually declines or normalizes spontaneously by end of induction cycle
	lymphadenopathy (8%)
	neutropenia (10%, severe 10%)
	thrombocytopenia (18%, severe 13%)
cardiac	arrhythmia (5%)
	palpitations (10%)
	sinus tachycardia (5%)
	tachycardia (55%)
ear and labyrinth	ear pain (8%)
	tinnitus (5%)
eye	blurry vision (10%)
	dry eye (8%)
	eye edema (5%)
	eye irritation (10%)
	eye pain (5%)
gastrointestinal	*emetogenic potential: low-moderate*[5]
	abdominal pain or tenderness, distension (8-38%, severe 3-8%)
	constipation (28%, severe 3%)
	diarrhea (63%)
	diarrhea, hemorrhagic (8%, severe 3%)
	dry mouth (8%)
	dyspepsia (10%)
	fecal incontinence (8%)
	flatulence (5%)
	gingival bleeding, mouth hemorrhage (5-10%)
	gastrointestinal hemorrhage (8%, severe 3%)
	hemorrhoids, proctalgia (5%)
	nausea (75%)
	oral mucosal blistering or inflammation, lip ulceration (5-8%)
	vomiting (58%)
general disorders and administration site	*extravasation hazard: irritant*[6]
	chest pain or discomfort (5-25%, severe 5%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
conditions	***chills*** (38%)
	edema (43-45%, severe 3%)
	facial edema (8%)
	fatigue (68%, severe 5%)
	injection site pain, inflammation, erythema, hemorrhage (5-23%, severe 3%)
	malaise (8%)
	pyrexia (63%, severe 5%)
hepatobiliary	jaundice (5%)
immune system	hypersensitivity (5%, severe 3%)
infections and infestations	bacterial infection (8%, severe 3%)
	herpes simplex, herpes zoster (8-13%)
	nasopharyngitis (8%)
	oral candidiasis (5%)
	pneumonia (13%, severe 5%)
	sepsis (5%, severe 5%)
	sinusitis (20%)
	upper respiratory tract infection (13%, severe 3%)
investigations	alkaline phosphatase increase (8%, severe 3%)
	ALT, AST increase (13-23%, severe 3-8%); usually resolves without treatment interruption
	BUN increase (8%)
	ECG abnormalitlies (23%)
	LDH increase (13%)
	QTc prolongation (33-68%, severe 3%)[2,7]; see paragraph following **Side Effects** table
	torsades de pointes (<1%)
	weight changes (8-13%)
metabolism and nutrition	appetite decrease (38%)
	hyperglycemia (45%, severe 13%)
	hyperkalemia (7-18%, severe 5%)
	hypocalcemia (4-10%)
	hypoglycemia (8%)
	hypokalemia (20-50%, severe 13%)
	hypomagnesemia (11-28%)
	tumour lysis syndrome (<1%)
musculoskeletal and connective tissue	arthralgia, myalgia (25-33%, severe 5-8%)
	asthenia (10%, severe 5%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	pain (5-23%, severe 3-10%)
neoplasms	skin, bladder, kidney, liver, prostate, and lung
nervous system	convulsion (8%, severe 5%)
	dizziness (25%)
	headache (63%, severe 3%)
	hypoesthesia (13%)
	lethargy (5%, severe 3%)
	paresthesia (33%, severe 5%)
	peripheral neuropathy (5%, severe 3%); usually resolves after end of treatment[8], but sometimes irreversible[2]
	somnolence (8%, severe 3%)
	tremor (13%)
psychiatric	agitation (8%)
	anxiety (33%, severe 3%)
	confusion (5%)
	depression (20%)
	insomnia (43%, severe 3%)
	mental status changes (5%, severe 3%)
renal and urinary	hematuria (13%)
	oliguria (5%)
	proteinuria (5%)
	renal impairment (8%, severe 3%)
	renal failure (8%)
	urinary incontinence (5%)
reproductive system and breast disorders	metrorrhagia, vaginal hemorrhage (8-13%)
respiratory, thoracic and mediastinal	***APL differentiation syndrome*** (23-30%)[1,2]; see paragraph following **Side Effects** table
	cough (65%); sometimes productive
	dyspnea (15-40%, severe 10%)
	epistaxis (25%)
	hemoptysis (8%, severe 3%)
	hypoxia (23%, severe 10%)
	lung infiltration (5%, severe 3%)
	nasal congestion, rhinitis, rhinorrhea (5%)
	oropharyngeal pain (40%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	pleural effusion (20%, severe 3%)
	tachypnea (8%)
	wheezing, rales, rhonchi (8-13%)
skin and subcutaneous tissue	blisters, lesions (5-8%)
	dermatitis (45%)
	dry skin (15%)
	ecchymosis, petechiae (8-20%)
	erythema, hyperpigmentation (8-13%)
	exfoliation (5%)
	hyperhidrosis (13%)
	night sweats (8%)
	pruritus (33%)
	urticaria (8%)
vascular	flushing (10%)
	hemorrhage (8%)
	hypertension (10%)
	hypotension (25%)
	pallor (10%)

Adapted from standard reference[2] unless specified otherwise.

Acute arsenic toxicity presents with convulsions, muscle weakness, confusion, and ECG abnormalities. Arsenic trioxide treatment should be stopped and chelation therapy considered. Dimercaprol has been used in the management of acute arsenic intoxication at a dose of 3 mg/kg intramuscularly every four hours until the immediate life-threatening toxicity subsides. ECG monitoring is recommended.[2]

APL differentiation syndrome (similar to retinoic acid-APL syndrome) may be experienced in up to 30% of patients with acute promyelocytic leukemia (APL) treated with arsenic trioxide and can be fatal.[2] It is observed mostly during induction treatment and is more likely to develop in patients who develop hyperleukocytosis.[1] Signs and symptoms include dyspnea, unexplained fever, weight gain, peripheral edema, unexplained hypotension, acute renal failure or congestive heart failure, and interstitial pulmonary infiltrates or pleuropericardial effusion with or without leukocytosis. Arsenic trioxide should be temporarily interrupted and high dose steroids initiated at the first signs of symptoms suggestive of this syndrome.[2] Consider hydroxyurea in situations of marked hyperleukocytosis (WBC count greater than 10 x 10^9/L).[4,9]

QT prolongation is expected with arsenic trioxide treatment and reported to develop gradually over a period of 6 to 24 days. Observed QT changes do not continue to increase with continued exposure to arsenic trioxide and are transient, reversing gradually following completion of therapy.[7] The changes are more prominent in patients with hypokalemia or hypomagnesemia.[1] QT prolongation can also lead to torsades de pointes (TdP). Torsades de pointes may be asymptomatic or experienced as dizziness, palpitations, syncope, or seizures. If sustained, TdP can progress to ventricular fibrillation and sudden cardiac death. Use arsenic cautiously in individuals with known risk factors for TdP, and correct electrolyte disturbances and other concomitant risk factors prior to treatment. Monitor ECG as indicated. Arsenic trioxide may be initiated in patients with QTc values of less than 430 msec (males) or 450 msec (females). Consider treatment interruption in patients who reach an absolute QT/QTc interval value greater

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than 500 msec during treatment. Patients who develop syncope, rapid, or irregular heartbeat may require hospitalization for monitoring. In these patients, arsenic trioxide should be interrupted until QTc interval regresses below 460 msec, electrolyte abnormalities are corrected, and syncope and irregular heartbeat cease.[2]

INTERACTIONS:

Concurrent therapy with drugs associated with QT/QTc interval prolongation or torsades de pointes should be avoided due to the risk of potentially fatal arrhythmias.[2]

Arsenic trioxide is a substrate for multidrug resistance-associated protein and P-glycoprotein. Strong inhibitors of these transporters may reduce the efflux of arsenic and increase its tissue concentration.[2]

Arsenic trioxide is an inducer of CYP 3A4 and CYP 2A, and possibly CYP 2B1/2, and may reduce the systemic concentration of substrates of these isoenzymes.[2]

SUPPLY AND STORAGE:

Injection: Teva Canada Ltd. supplies arsenic trioxide as 12 mg ready-to-use, single-use (preservative free) vials in a concentration of 2 mg/mL. Store at room temperature.[10]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information: Arsenic trioxide must not be mixed with or administered in the same intravenous line as other drug products.[2]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	no information found
Intermittent infusion[2,8,11-15]	***over*** 1-***2 h***; may be extended up to 4 h if acute vasomotor reactions are observed[2]
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

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Revised: 1 June 2021

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	n/a[2,8,12-15]:	*induction:* ***0.15 mg/kg IV once daily*** until bone marrow remission (total induction dose should not exceed 60 doses) *consolidation* (usually beginning 1-6 weeks after completed induction): ***0.15 mg/kg*** (range 0.075-0.15 mg/kg) ***IV once daily, given 5 days per week*** (maximum 25 doses over a period up to 5 weeks).
Concurrent radiation:	no information found	
Dosage in myelosuppression:	modify according to protocol by which patient is being treated	
Dosage in renal failure:	all patients with renal impairment should be monitored for toxicity; patients with creatinine clearance less than 30 mL/min may require dose reduction.[2]	
	Calculated creatinine clearance = $\frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{Serum Creatinine in } \mu\text{mol/L}}$ * For males N=1.23; for females N=1.04	
Dosage in hepatic failure:	all patients with hepatic impairment should be monitored for toxicity; patients with severe hepatic failure may require dose reduction[2]; modify according to protocol by which patient is being treated.	
Dosage in dialysis:	no information found	

Children:

	Cycle Length:	
Intravenous:	n/a[3,16]	*induction*: 0.15 mg/kg IV once daily (total induction dose should not exceed 60 doses) *consolidation* (beginning 3-6 weeks after completed induction): 0.15 mg/kg IV once daily (maximum 25 doses over a period up to 5 weeks).

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