

DRUG NAME: Thiotepa

SYNONYM(S): TESPA, ¹ TSPA ¹

COMMON TRADE NAME(S): TEPADINA®

CLASSIFICATION: alkylating agent

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

MECHANISM OF ACTION:

Thiotepa, a derivative of nitrogen mustard, acts as a polyfunctional alkylating agent. Alkylation takes place through the formation of a highly reactive ethylenimine radical. This radical likely forms a cross-linkage between two strands of DNA, ² interfering with DNA, RNA, and protein synthesis. ^{2,1,3} These actions do not appear to be cell cycle phase-specific. Thiotepa has immunosuppressive properties. ¹ Intracavitary (intra-pleural, -pericardial, and -peritoneal) administration of thiotepa also produces an inflammatory reaction on serous membranes with a resulting sclerosing effect. ¹

PHARMACOKINETICS:

Oral Absorption	unreliably absorbed from GI tract due to acid instability; not administered orally	
Distribution	peak plasma concentrations occur immediately; lipid-soluble ⁴	
	highly lipophilic; after IV, fits a two compartment model with rapid distribution phase	
	cross blood brain barrier? ⁵⁻⁷	yes (thiotepa and triethylenephosphoramidate (TEPA) metabolite) ^{8,4} ; after IV, CSF and plasma concentrations of TEPA exceed those of parent compound
	volume of distribution ^{8,1,9}	41-75 L/m ²
	plasma protein binding	8-29%
Metabolism	rapid and extensive hepatic metabolism via oxidative desulfuration by CYP 3A4 and CYP 2B6 AND conjugation with glutathione ⁸	
	active metabolite(s)	-TEPA (major); via CYP 3A4 and CYP 2B6 thiotepa-mercaptopurinate; via conjugation with glutathione
	inactive metabolite(s)	yes
Excretion	also excreted in skin and sweat (percentage of total dose unknown) with high-dose IV	
	urine	0.5% (thiotepa and monochlorotepa); 11% (TEPA and thiotepa-mercaptopurinate)
	feces	no information found
	terminal half life ^{2,3}	1.4-3.7 h (thiotepa); 4.9-17.6 (TEPA)
	clearance ⁸	11.4 - 23.2 L/h/m ²

Adapted from standard reference ^{8,1} unless specified otherwise.

USES:

Primary uses:

- *High-dose for consolidation regimen prior to stem cell transplant (for CNS lymphoma)
- Malignant meningeal neoplasms (intrathecal) ¹⁰

Other uses:

- Bladder cancer (intravesical) ¹⁰
- Breast cancer ¹⁰
- Intracavitary effusions secondary to malignancy ¹⁰
- Ovarian cancer ¹⁰

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- **cardiac related events** (e.g., arrhythmia, CHF, cardiomyopathy) are reported; use thiotepa with caution in patients with a history of cardiac disease ⁸
- risk of **hepatic veno-occlusive disease** may be increased in patients who have received prior radiation therapy, prior stem cell transplant, or more than 2 cycles of chemotherapy ⁸
- **pulmonary toxicity** caused by thiotepa may be additive with toxicity caused by other agents (e.g., busulfan, fludarabine, etc.) ⁸
- **neurotoxicity** may be greater in patients with prior brain or craniospinal irradiation
- **skin reactions** (e.g., depigmentation, dermatitis) have occurred following **accidental exposure** to thiotepa; safe handling precautions should be followed ^{2,8}
- avoid concomitant **live** virus or bacterial **vaccines** until the immunosuppressive effects of thiotepa have resolved ⁸
- **obese** patients should be closely monitored for toxicity because dosing based on total body weight may result in higher than expected thiotepa exposure; consider using adjusted body weight for calculating BSA ⁸

Carcinogenicity: Thiotepa is carcinogenic. [Treatment-related secondary malignancies, including myelodysplastic syndrome and acute non-lymphocytic leukemia, have been reported.](#) ⁸

Mutagenicity: Mutagenic in Ames test and mammalian *in vitro* mutation test. ² Thiotepa is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests. ²

Fertility: Amenorrhea and impaired spermatogenesis have been reported. [Fertility preservation strategies should be discussed prior to treatment \(if applicable\) as thiotepa commonly causes infertility in male and female patients.](#) ⁸

Pregnancy: [Thiotepa has been shown to be teratogenic and to cause fetal death in animal studies at doses lower than those used in humans. Do not use during pregnancy and use effective contraception if either the patient or their partner is of child-bearing potential.](#) ⁸

Breastfeeding is not recommended due to the potential secretion into 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. ¹¹

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
allergy/immunology	allergic reactions (1-10%) ³
blood/bone marrow/ febrile neutropenia	myelosuppression (>10%) ³ ; cumulative ¹ and dose-related; may occur up to 30 days after treatment ¹ ; deaths reported
	anemia
	leukopenia; nadir ¹ typically days 10-14
	thrombocytopenia; onset ³ typically days 7-10, nadir day 14, recovery day 28
constitutional symptoms	fatigue (1-10%) ³
	fever (1-10%) ³ ; secondary to tumour breakdown
dermatology/skin	extravasation hazard: none ¹²
	alopecia (1-10%) ³
	discharge from subcutaneous lesions; secondary to tumour breakdown
	hyperpigmentation ³ (1-10%) ³ ; with high-dose BMT therapy ³
	rash (1-10%) ³ ; pruritis ³ (1-10%) ³ ; urticaria (1-10%) ³ ; dermatitis
	skin reactions including contact dermatitis and depigmentation ³ ; with topical exposure ³
gastrointestinal	emetogenic potential: low ¹³
	anorexia (1-10%) ³
	nausea and vomiting (1-10%) ³
	stomatitis, mucositis; dose-limiting with high-dose BMT therapy ^{3,14}
hemorrhage	hemorrhage; secondary to myelosuppression; deaths have occurred
infection	septicemia; deaths have occurred
metabolic/laboratory	serum transaminitis and hyperbilirubinemia; with high-dose BMT therapy ³
	hyperuricemia ^{1,3} (1-10%) ³
musculoskeletal	weakness (1-10%) ³
neurology	confusion, inappropriate behavior; with high-dose BMT therapy ³
	dizziness (1-10%) ³
	somnolence; with high-dose BMT therapy ³
ocular/visual	blurred vision
	conjunctivitis (1-10%) ³
pain	abdominal pain
	dysuria
	headache (1-10%) ³
	injection site pain (>10%) ³
renal/genitourinary	cystitis ⁸
	dysuria ⁸
	urinary retention (1-10%) ³

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
secondary malignancy	myelodysplastic syndrome and acute non-lymphocytic leukemia (<1%) ³
sexual/reproductive function	amenorrhea (1-10%) ³ ; impaired spermatogenesis

Adapted from standard reference² unless specified otherwise.

Intrathecal administration is typically well tolerated. Systemic toxicities are infrequent with the exception of myelosuppression. Neurologic toxicities may occur, including weakness, paresthesia¹⁵, and aseptic chemical meningitis (characterized by fever, headache, nausea and vomiting, meningismus, photophobia, and dehydration). Better drug exposure may be achieved if given IV because thiotepa diffuses rapidly out of the CNS and the active metabolite TEPA is not formed in the CNS.⁴

Intravesical administration may cause systemic toxicities due to absorption, including myelosuppression (3-54%) and allergic reactions (3%). Absorption is variable (e.g., 10-100%) and is increased by multiple tumours, tumour infiltration, mucosal inflammation, and reflux of urine from the bladder into the ureter. Dose-dependant chemical cystitis may occur (1-69%); however, hemorrhagic cystitis is rare. Delay therapy or dose reduce to manage irritative symptoms. Rarely, eosinophilic cystitis, azoospermia, and non-lymphocytic leukemia and myelodysplastic syndrome have been reported.^{16,17,2,18,14,1,3,19}

Gastrointestinal toxicity is very common with high dose thiotepa, including severe nausea, vomiting, and diarrhea. Grade 3 or 4 mucositis occurs in the majority of patients. Management of mucositis may require total parenteral nutrition.⁸

Profound **myelosuppression** (e.g., anemia, neutropenia, and thrombocytopenia) is a primary dose-limiting toxicity with conventional thiotepa dosing and occurs in all patients with high-dose thiotepa. Median time for recovery is 8-18 days for platelets and 8-11 days for neutrophils. Myelosuppression may be persistent and refractory, and fatalities due to infections and hemorrhage have been reported. Consider use of prophylactic anti-infectives during the neutropenic period. Platelet and red blood cell support, plus growth factors (e.g., GCSF) may also be required to achieve count recovery.⁸

Thiotepa can cause severe **neurotoxicity**. Because of its lipophilicity, thiotepa is able to cross the blood-brain barrier after IV administration and achieve cerebrospinal fluid concentrations equivalent to plasma concentrations. Patients with prior brain or craniospinal irradiation may experience greater neurotoxicity. Cases of leukoencephalopathy have been reported and are sometimes fatal. Many neuropsychiatric events have been associated with thiotepa including: cognitive disorder, memory deficit, confusion, delirium, agitation, hallucination, anxiety, extrapyramidal disorders, convulsions, dizziness, headache, blurred vision, encephalopathy, and paresthesias.⁸

Thiotepa is excreted through the **skin** and has been detected in the sweat of patients receiving high dose thiotepa. Skin toxicity may include rash (predominantly involving the axillae, groin, and elbows), pruritus, urticaria, erythrodermic psoriasis, alopecia, and pigmentation disorders, as well as Stevens-Johnson syndrome and toxic epidermal necrolysis. Skin reactions have also been reported following accidental (i.e., occupational) exposure to thiotepa.⁸

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
aprepitant ²⁰	delayed and decreased exposure to TEPA (20%)	inhibition of CYP enzymes (likely 3A4 and 2B6)	minor clinical importance due to large inter- and intra-individual variability in thiotepa clearance
phenytoin ^{21,22}	increased rate of thiotepa conversion to TEPA	strong induction of CYP 2B6 enzyme by phenytoin	avoid concurrent use; if used consider dose reduction of thiotepa
succinylcholine, ² pancuronium ²¹	prolonged apnea may occur	thiotepa may inhibit pseudocholinesterase activity	caution; consider avoiding concurrent use

Thiotepa is a major CYP 2B6 inhibitor; therefore, serum levels/effects of drugs or herbs that are CYP 2B6 substrates may be increased. ³

SUPPLY AND STORAGE:

Injection:

Hikma Canada Limited supplies thiotepa as 15 mg and 100 mg single use (preservative free) vials of lyophilized powder. Refrigerate. Protect from light. ²³

SteriMax Inc. supplies thiotepa as 15 mg and 100 mg single use (preservative free) vials of lyophilized powder. Refrigerate. Protect from light. ²⁴

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:

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	no information found
Intramuscular	has been used ²⁵
Direct intravenous	has been used ²⁵
Intermittent infusion	over 2-4 h (via a central catheter); administer with a 0.2 micron inline filter ^{8,26}
Continuous infusion	has been used ²⁷⁻²⁹
Intraperitoneal	has been used ³⁰

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

Intrapleural	has been used ²⁵
Intrapericardial	no information found
Intrathecal ^{31,25}	<i>dilute in small volume (6 mL)</i> or to a concentration ¹ of 1 mg/mL with <i>preservative-free NS</i> ³²
Intra-arterial	no information found
Intravesical	has been used ²³
Intralesional	no information found

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***

<i>Intravenous:</i>	Cycle Length: 1-4 weeks ¹⁻³ :	0.3-0.4 mg/kg IV for one dose on day 1 (total dose per cycle 0.3-0.4 mg/kg)
	2-4 weeks ^{1,3} :	0.2 mg/kg or 6-8 mg/m ² IV once daily for 4-5 consecutive day starting on day 1 (total dose per cycle 0.8-1.0 mg/kg or 24-40 mg/m ²)
	n/a ⁸ :	185-370 mg/m ² IV once daily as 1 to 2 infusions over 2 to 3 consecutive days prior to autologous stem cell transplant Max cumulative dose during consolidation regimen = 750 mg/m ²
<i>Intracavitary:</i>	≥1 week ^{2,3} :	0.6-0.8 mg/kg or 30-60 mg instilled intracavitary for one dose on day 1 (total dose per cycle 0.6-0.8 mg/kg or 30-60 mg) • 15-30 mg intrapericardially has been used
<i>Intramuscular:</i>	various schedules ^{1,3} :	15-30 mg IM for one dose on day 1
<i>Intrathecal:</i>	n/a ^{33,34,3,32} :	<i>12 mg</i> (range 10-15 mg) <i>IT for one dose once or twice weekly</i> (maximum two IT injections per week) • diffuses rapidly out of the CSF, ^{5,35} active metabolite TEPA is not formed ⁷ and better drug exposure may be achieved if given IV ³⁶
	n/a ^{1,3} :	1-11.5 mg/m ² IT for one dose once or twice weekly

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

	Cycle Length:	
<i>Intravesical:</i>	n/a ^{2,9,37} ;	60 mg (range 30-60 mg) instilled intravesically for one dose on days 1, 8,15, and 22 (total dose per cycle 240 mg) <ul style="list-style-type: none"> • cycle may be repeated if needed; caution due to the risk of myelosuppression • after initial treatment, monthly installations have also been used
<i>Intralesional</i>	n/a ¹ :	0.6-0.8 mg/kg injected directly into the tumour for one dose on day 1 followed by maintenance doses of 0.07-0.8 mg/kg injected into the tumour every 1-4 weeks
<i>Concurrent radiation:</i>	has been used ²	
<i>Dosage in myelosuppression:</i>		modify according to protocol by which patient is being treated ² ; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"
<i>Dosage in renal failure:</i>		no information found; monitor for increased toxicity ⁸
<i>Dosage in hepatic failure:</i>		no information found; monitor for increased toxicity as thiotepa is mainly metabolized by the liver ⁸
<i>Dosage in dialysis:</i>		removed by dialysis ²
<u>Children:</u>		safety and effectiveness have not been established ² ; has been used ^{3,6}

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