DRUG NAME: Thiotepa

SYNONYM(S): TESPA,[1] TSPA[1]

COMMON TRADE NAME(S):

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.[2] Alkylation takes place through the formation of a highly reactive ethylenimine radical.[2] This radical likely forms a cross-linkage between two strands of DNA,[2] interfering with DNA, RNA, and protein synthesis.[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	variable as unstable in acidic pH; therefore, not administered orally	
Distribution	peak plasma concentrations occur immediately; lipid-soluble,[4] variable absorption occurs through serous membranes and from IM injection, peritoneum (80-100%), bladder (10-100%) IT: diffuses rapidly out of the CSF[5,6]	
	cross blood brain barrier?[5,7,8]	yes; triethylenephosphoramide metabolite (TEPA): yes[4]
	volume of distribution[1,9]	0.3-1.6 L/kg
	plasma protein binding	8-29%; TEPA more extensively bound
Metabolism	extensive hepatic metabolism; involves the hepatic microsomal enzyme oxidation system and glutathione conjugation[9,10]; thiotepa is metabolized to TEPA by CYP 3A4 (major) and CYP 2B6 (minor)[10]	
	active metabolite(s)[2]	yes; including TEPA; when given IT, TEPA is not formed in the CNS
	inactive metabolite(s)	yes
Excretion	biphasic elimination; renal <1%; excreted in sweat to an appreciable extent with high-dose IV	
	urine	0.1-2%; TEPA: 4%; unidentified metabolites with alkylating activity: 13-24%
	feces	no information found
	terminal half life[2,3]	1.2-2.9 h; TEPA: 10-21 h
	clearance	180-780 mL/min/m^2

Adapted from standard reference[1] unless specified otherwise.

USES:

Primary uses:
*Bladder cancer (intravesical)
Malignant meningeal neoplasms[1,11] (intrathecal)

Other uses:
*Breast cancer
High-dose for myeloablation prior to bone marrow transplant[9]
*Intracavitary effusions secondary to malignancy
*Ovarian cancer

*Health Canada approved indication

SPECIAL PRECAUTIONS:

- existing hepatic or renal damage[2]; see **DOSAGE GUIDELINES**
- skin reactions including depigmentation and dermatitis have occurred after accidental exposure; safe handling precautions should be followed when handling thiotepa; if skin contact occurs, wash the area thoroughly with soap and water; if mucous membrane contact occurs, flush thoroughly with water[2]

Carcinogenicity: Thiotepa is carcinogenic.[2]

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.[2]

Pregnancy: FDA Pregnancy Category D.[2] There is positive evidence of human fetal risk,[2] but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

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.[12]

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*[13]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	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*[14]
	anorexia (1-10%)[3]
	nausea and vomiting (1-10%)[3]
	stomatitis, mucositis; dose-limiting with high-dose BMT therapy[3,15]
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	urinary retention (1-10%)[3]
secondary malignancy	myelodysplastic syndrome and acute non-lymphocytic leukemia (<1%)[3]
sexual/reproductive function	amenorrhea (1-10%)[3]; impaired spermatogenesis

Adapted from standard reference[2] unless specified otherwise.

Intrathecal administration is typically well tolerated.[4] Systemic toxicities are infrequent with the exception of myelosuppression.[4] Neurologic toxicities including weakness and paresthesia[16] and aseptic chemical meningitis, characterized by fever, headache, nausea and vomiting, meningismus, photophobia, and dehydration may occur.[4] 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[17,18] (3-54%; deaths reported[2]) and allergic reactions[19] (3%). Absorption is variable[15,17] (10-100%) and is increased by multiple tumours, tumour infiltration, mucosal inflammation, and reflux of urine from the bladder into the ureter.[1,17] Dose-dependant chemical cystitis (1-69%)[3,17,18] may occur; however, hemorrhagic cystitis is rare.[2,18] Delay therapy

or dose reduce to manage irritative symptoms.[17] Rarely, eosinophilic cystitis,[20] azoospermia,[18] and non-lymphocytic leukemia and myelodysplastic syndrome have been reported.[17]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
aprepitant[21]	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[22,23]	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[22]	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: Bedford Laboratories supplies thiotepa as 15 mg single-use vials of nonpyrogenic, sterile, lyophilized powder.[2]

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

SOLUTION PREPARATION AND COMPATIBILITY:

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

Additional information: Do not use reconstituted solutions that are opaque or contain a precipitate after filtration thorough a 0.22 micron filter.[2] Filtration to be done by pharmacy prior to dispensing; **see Chemotherapy Preparation and Stability chart** for details**.**

Reconstituted thiotepa may be mixed with lidocaine,[3] 2% procaine hydrochloride, or 0.1% epinephrine for local administration.[24]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous	has been used[3]; no advantage over IV direct
Intramuscular	has been used[1]; no advantage over IV direct
Direct intravenous	over 1-2 minutes[3]
Intermittent infusion	over 10-60 minutes[3]
Continuous infusion	has been used[25-27]

BCCA administration guideline noted in ***bold***, ***italics***

Intraperitoneal	dilute to a larger volume[1,2,7] (e.g., ≤2L)
Intrapleural	dilute to 10-60 mL in SWI, NS, or D5W[7,28]
Intrapericardial	dilute to 10-20 mL in NS or D5W[7]
Intrathecal	***by physician only***[27]***; dilute in small volume (6 mL) or*** to a concentration[1] of 1 mg/mL with ***preservative-free NS***[11]; higher concentrations have been used[29]
Intra-arterial	no information found
Intravesical	in 30-60 mL of NS; dwell time 2 h; dehydrate patient for 8-12 h prior to treatment; may rotate position every 15 minutes for better contact[1,2]
Intralesional	investigational[1,24]

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*:**

BCCA usual dose noted in ***bold, italics***

	Cycle Length:	
**Intravenous:*	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)
Intracavitary:	≥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
Intramuscular:	various schedules[1,3]:	15-30 mg IM for one dose on day 1
Intrathecal:	n/a[3,11]:	***12 mg*** (range 10-15 mg) ***IT for one dose once or twice weekly*** ***(maximum two IT injections per week)*** • diffuses rapidly out of the CSF,[5,6] active metabolite TEPA is not formed[8] and better drug exposure may be achieved if given IV[30]
	n/a[1,3]:	1-11.5 mg/m^2 IT for one dose once or twice weekly
Intravesical:	n/a[2,9,28]:	60 mg (range 30-60 mg) instilled intravesically for one dose on days 1, 8,15, and 22 (total dose per cycle 240 mg) • cycle may be repeated if needed; caution due to the risk of myelosuppression • after initial treatment, monthly installations have also been used

BCCA usual dose noted in ***bold, italics***

	Cycle Length:	
Intralesional	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
Concurrent radiation:	has been used[2]	
Dosage in myelosuppression:	modify according to protocol by which patient is being treated[2]; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"; the manufacturer recommends discontinuing therapy[2] if the leukocyte count falls to $\leq 3 \times 10^9$/L or if the platelet count falls $\leq 150 \times 10^9$/L	
Dosage in renal failure:	dose reduction may be required[2,3]; no details found	
Dosage in hepatic failure:	limited data suggests clearance may be decreased[1]; use with caution[2]; dose reduction may be required[2]; no details found	
Dosage in dialysis:	removed by dialysis[2]	

Children:

safety and effectiveness have not been established[2]; has been used[3,7]

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