DRUG NAME: Treosulfan

SYNONYM(S):

COMMON TRADE NAME(S): TRECONDYV®

CLASSIFICATION: alkylating agent

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

MECHANISM OF ACTION:

Treosulfan is the pharmacologically inactive prodrug of a bifunctional alkylating agent. Structurally, treosulfan is related to busulfan. The cytotoxic activity of treosulfan is attributed to its spontaneous (pH dependent) conversion to active epoxide compounds which cause stem cell depletion and broad antineoplastic effects through alkylation of the DNA and other biological molecules. The immunosuppressive effects of treosulfan are attributed to its toxicity against primitive and committed hematopoietic progenitor cells, T and NK cells, as well as the reduction in cellularity of primary and secondary lymphatic organs.[1]

PHARMACOKINETICS:

Absorption	peak plasma levels are reached at the end of the infusion	
Distribution	rapidly distributed in the body	
	cross blood brain barrier?	limited penetration
	volume of distribution	20-47 L
	plasma protein binding	no information found
Metabolism	treosulfan is converted spontaneously (non-enzymatically) into its active compounds	
	active metabolite(s)	(2S,3S)-1,2-epoxybutane-3,4-diol-4-methanesulfonate) and L-diepoxibutane (2S,3S)-1,2:3,4-diepoxybutane)
	inactive metabolite(s)	none
Excretion	first order elimination process fitted by a two-compartment model	
	urine	14-40% of the dose (unchanged) within 24 h
	feces	no information found
	terminal half life	~2 h
	clearance	150-300 mL/min
Sex	comparable in male and female patients	
Elderly	small differences in pharmacokinetic parameters not considered clinically significant	

Adapted from standard reference[1] unless specified otherwise.

USES:

Primary uses:

*Conditioning regimen for stem cell transplantation

Other uses:

Ovarian cancer[2]

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to treosulfan or busulfan[3]

Caution:
- avoid ***live vaccines*** during treatment to prevent generalized infection following immunization[1]
- ***mucositis*** is common; good oral hygiene and prophylaxis with topical antimicrobials, barrier protectants, ice chips, etc. are recommended[1]

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.[4-6]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***febrile neutropenia*** (11%)
	myelosuppression/pancytopenia (100%); see paragraph following ***Side Effects*** table
cardiac	arrhythmias (atrial fibrillation, sinus arrhythmia) (18%)
	cardiac failure (1%)
ear and labyrinth	vertigo (4%)
gastrointestinal	*emetogenic potential:* moderate[7]***;*** highly emetogenic if high dose for stem cell/bone marrow transplantation[8-10]
	abdominal pain (11-17%, severe 2%)
	constipation (12%, severe <1%)
	diarrhea (15-35%, severe 2%)
	nausea (28-39%, severe 3%)
	stomatitis (36-67%, severe 6%)
	vomiting (22-42%, severe 1%)
general disorders and administration site conditions	*extravasation hazard:* irritant[11]
	administrative site conditions (56%); no specific antidote for extravasation
	chills (7%, severe <1%)
	edema, limb (23%, severe <1%)
	edema, localized (6%, severe <1%)
	fatigue (12-15%, severe 1%)
	fever (34%, severe 1%)
	pyrexia (13%)
hepatobiliary	***hepatotoxicity*** (26%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
immune system	allergic reaction (6%, severe <1%)
infections and infestations	***infection*** (12-27%, severe 15%)
investigations	ALT increase (9-11%, severe 5%)
	AST increase (9%, severe 4%)
	gamma-glutamyltransferase (7%, severe 4%)
	hyperbilirubinemia (9-18%, severe 3%)
	weight gain (7%)
metabolism and nutrition	anorexia (9%, severe 2%)
	hypomagnesemia (5%)
musculoskeletal and connective tissue	arthralgia (10%, severe 1%)
	back pain (15%, severe 3%)
	bone pain (14%, severe 1%)
	extremity pain (9%, severe 1%)
neoplasms	secondary malignancy
nervous system	headache (16%, severe 1%)
	dizziness (6%)
reproductive system and breast disorders	scrotal erythema
respiratory, thoracic and mediastinal	dyspnea (5%, severe 1%)
	epistaxis (7%)
skin and subcutaneous tissue	alopecia (10%)
	pruritus (6-10%, severe <1%)
	purpura (5%)
	rash, maculopapular (12%, severe 1%)
vascular	hypertension (14%, severe 8%)
	hypotension (7%, severe 2%)

Adapted from standard reference[1] unless specified otherwise.

Profound ***myelosuppression*** with pancytopenia is the desired therapeutic effect of high-dose treosulfan-based conditioning treatments, and occurs in all patients.[1] When given in lower doses without stem cell support, myelosuppression, manifested by a reduction in leukocytes, platelets and hemoglobin, is dose limiting and usually reversible. Leukocytes and platelets usually return to baseline after 21-28 days.[3,12] Mean duration of neutropenia is 14-18 days in adults and 21-24 days in pediatric patients.[1] If treosulfan is used for indications other than allogeneic stem cell transplantation, treatment should be delayed until blood counts recover, with subsequent treatments restarted at a lower dose. Lower initial doses are suggested for patients with medical risk factors such as previous or current myelosuppressive treatments, radiation, or pre-existing bone marrow suppression.[3] Inhibition of bone marrow function is cumulative; therefore, blood counts should be monitored at shorter intervals after the second cycle, especially if used concurrently with radiotherapy or other myelosuppressive treatments.[12]

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INTERACTIONS:

Treosulfan is an inhibitor of CYP 3A4, CYP 2C19, and P-gp. However, based on pharmacokinetic modeling of treosulfan, the potential for interaction is low. For substrates of CYP 3A4 or CYP 2C19 with a narrow therapeutic index, if coadministration cannot be avoided, consider administering the substrate either 2 hours before or 8 hours after the treosulfan conditioning regimen.[13]

SUPPLY AND STORAGE:

Injection: Medexus Inc. supplies treosulfan injection as 1 g and 5 g single use (preservative free) vials of lyophilized powder. Store at room temperature.[1]

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:

- do NOT refrigerate reconstituted or diluted treosulfan as solution may precipitate; discard if precipitates are present[1]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	no information found
Intermittent infusion	***over 2 hours***[1]; has been given over 15-30 min when used in cyclical chemotherapy regimens[14]
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

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.

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***Adults*:**

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

Intravenous:	Cycle Length: n/a[1,15-17]	***12 g/m²*** (range 10-14 g/m²) ***IV for one dose on three consecutive days*** (e.g., days -6, -5, -4) ***before stem cell transplantation*** (total dose 36 g/m² [range 30-42 mg/m²])
	3-4 weeks[2,3,14]:	8 g/m² (range 3-9 g/m²) IV for one dose on day 1 (total dose per cycle 8 g/m² [range 3-9 g/m²])
Concurrent radiation:	no information found	
Dosage in renal failure[1]:	mild to moderate renal impairment: no adjustment required; although excreted in urine, no influence of renal function on overall clearance was observed[1] severe impairment: no information found	
Dosage in hepatic failure[1]:	mild to moderate impairment: no adjustment required severe impairment: no information found	
Dosage in dialysis:	no information found	

Children:

Intravenous:	Cycle Length: n/a[1]:	10 g/m² (range 10-14 g/m²) IV for one dose on three consecutive days (e.g., days -4, -3, -2) before stem cell transplantation (total dose 30 g/m² [range 30-42 mg/m²])

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