DRUG NAME: Treosulfan

SYNONYM(S):

COMMON TRADE NAME(S):

CLASSIFICATION: alkylating agent

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

MECHANISM OF ACTION:

Treosulfan is an alkylating agent related to busulfan. The *in vivo* conversion of treosulfan to active epoxide compounds is thought to provide the basis for its activity, as the epoxides react with the nucleophilic centres of DNA via alkylation.[1,2]

USES:

Primary uses:

Other uses:
Ovarian cancer
Stem cell transplantation

*Health Canada approved indication

SPECIAL PRECAUTIONS:

- contraindicated in patients who have a history of sensitivity to treosulfan or busulfan[3]
- myelosuppression is the dose limiting side effect, and lower initial doses are suggested for patients with a history of previous myelosuppressive treatment, including radiation, or severe and lasting bone marrow depression.[1,3] See paragraph after **Side Effects** table.
- to prevent hemorrhagic cystitis, patients are advised to increase fluid intake for up to 24h after infusion[1]
- avoid live vaccines during treatment to prevent generalized infection following immunization[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.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	not known
blood/bone marrow/ febrile neutropenia	***anemia*** (>10%)
	leucocytopenia (>10%)
	myelosuppression (49%)[3]; see paragraph following **Side Effects** table
	thrombocytopenia (>10%)
cardiovascular (general)	cardiomyopathy
constitutional symptoms	flu-like symptoms
dermatology/skin	*extravasation hazard: vesicant*[1,4]; may result in painful inflammatory reactions, tissue damage may occur[1]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	alopecia (16%)[3]; usually mild
	bronze skin pigmentation (30%)[3]; usually mild[3]
	erythema
	psoriasis trigger
	scleroderma
	urticaria
endocrine	Addison's disease
gastrointestinal	*emetogenic potential: low-moderate*[5]
	nausea (45%)[3]; usually mild and resolves after treatment
	vomiting (45%)[3]; usually mild and resolves after treatment
hepatobiliary/pancreas	jaundice[3]
infection	risk of mycotic, viral, bacterial infection
	pneumonia
metabolic/laboratory	hypoglycemia
neurology	depression[3]
	paresthesia
pulmonary	alveolitis; requires permanent cessation of treatment
	pulmonary fibrosis; requires permanent cessation of treatment
renal/genitourinary	hemorrhagic cystitis; increase fluid intake for up to 24 h after infusion
secondary malignancy	acute non-lymphocytic leukemia (1%); risk may increase with cumulative dose
	myelodysplastic syndrome (<1%)
	myeloma (<1%)
	myeloproliferative disorder (<1%)

Adapted from standard reference[1] unless specified otherwise.

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.[1,3] 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.[1]

SUPPLY AND STORAGE:

Injection: medac UK supplies treosulfan injection as 1 g or 5 g vials of powder for injection. Store at room temperature.[1]

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: Reconstitution instructions must be carefully followed to avoid problems.[1] Refer to product insert.

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	not used due to corrosive nature
Intramuscular	not used due to corrosive nature
Direct intravenous[1]	doses ≤3 g/m^2 only; into tubing of running IV; see ***Prevention and Management of Extravasation of Chemotherapy***
Intermittent infusion[1]	doses >3 g/m^2: give at rate of 3 g/m^2 every 5-10 min or 8 g/m^2 over 30 min
Continuous infusion	no information found
Intraperitoneal[1]	has been given
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.

***Adults*:**

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

Intravenous:	Cycle Length: 1-4 weeks:[1,3]	3-8 g/m^2 IV for one dose on day 1; doses up to 9 g/m^2 have been used
	n/a[6-8]	10-14 g/m^2 IV for one dose on days -6,-5 and-4 prior to stem cell transplantation (total dose per treatment 30-42 g/m^2)

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4. BC Cancer Agency Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer Agency; 01 December 2007.
5. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 March 2008.
6. Baronciani D, Rambaldi A, Iori AP, et al. Treosulfan/fludarabine as an allogeneic hematopoietic stem cell transplant conditioning regimen for high-risk patients. Am J Hematol 2008;83:717-720.
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8. Kroger N, Shimoni A, Zabelina T, et al. Reduced-toxicity conditioning with treosulfan, fludarabine and ATG as preparative regimen for allogeneic stem cell transplantation (alloSCT) in elderly patients with secondary acute myeloid leukemia (sAML) or myelodysplastic syndrome (MDS). Bone Marrow Transplant 2006;37(4):339-344.