# DRUG NAME: Teniposide

**SYNONYM(S):** 4'-demethylepipodophyllotoxin[1]; ETP[2]; VM-26[2]

**COMMON TRADE NAME(S):** VUMON®

**CLASSIFICATION:** Topoisomerase II inhibitor

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

## MECHANISM OF ACTION:

Teniposide is an epipodophyllotoxin, structurally and pharmacologically related to etoposide.[2] Teniposide inhibits type II topoisomerase resulting in single- and double-stranded DNA breaks.[1,3] It does not intercalate into nor bind strongly to DNA.[2] Teniposide arrests cell growth in the late S2 phase or early G2 phase of the cell cycle, preventing cells from entering mitosis.[1,3]

## PHARMACOKINETICS:

| | | |
|---|---|---|
| Oral Absorption | no information found | |
| Distribution | distribution half-life approximately 1 h | |
| | cross blood brain barrier?[4,5] | yes (<5%) |
| | volume of distribution[3,6] | 8-44 L/m² |
| | plasma protein binding | > 99% |
| Metabolism | extensively hepatic (86%)[3,4,7] | |
| | active metabolite(s) | no information found |
| | inactive metabolite(s) | no information found |
| Excretion | possible association between increased serum alkaline phosphatase or gamma-glutamyltransferase levels and decreased teniposide clearance[2,5,6] | |
| | urine[6] | 44% (4-12% as unchanged drug) |
| | feces[3,6] | ≤10% |
| | terminal half life | 6-20 h |
| | clearance[4,6] | 10.3 mL/min/m² |
| Children | clearance more rapid than in adults[8]; volume of distribution[3] 3-11 L/m² | |

Adapted from standard reference[1] unless specified otherwise.

## USES:

***Primary uses:***
*Neuroblastoma
*Lymphoma, non-Hodgkin's
*Leukemia, acute lymphocytic

***Other uses:***
Retinoblastoma[4]
Leukemia, acute myelogenous[4]
Multiple myeloma [4]
Lymphoma, Hodgkin's[5]
Rhabdomyosarcoma[5]
Soft tissue sarcoma[5]
Ewing's sarcoma[5]
Germ cell tumour[5]
Brain tumour[5]

*Health Canada approved indication

## SPECIAL PRECAUTIONS:

***Contraindications:***
- history of hypersensitivity reaction to teniposide, benzyl alcohol, or Cremophor EL®[1]
- Cross reactivity to etoposide has been reported in patients with hypersensitivity reactions to teniposide[9]; however there is still debate about the existence of true cross reactivity.[10]

***Caution:***
- Concurrent medication should be carefully reviewed for potential drug interactions, particularly with CYP 3A4, CYP 2C9 and P-glycoprotein (PgP); see paragraphs in **Interactions** section.[3,11,12]

***Special populations:***
- Down's Syndrome patients are more sensitive to myelosuppressive chemotherapy and may require initial dose reduction at 50% of the usual dose.[1,4]
- Neuroblastoma or brain tumour patients may experience a higher incidence of hypersensitivity reactions.[1,2]
- Newborns may experience toxicity to products containing benzyl alcohol. Caution is suggested in pediatric patients.[1,13]

***Carcinogenicity:*** The risk of secondary leukemia was associated with cumulative epipodophyllotoxin doses of 1.2-6 g/m² or greater.[1,14]

***Mutagenicity:*** Mutagenic in Ames test and mammalian *in vitro* mutation tests.[1,2] Teniposide is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[1,2]

***Fertility:*** Preclinical data demonstrates that teniposide may disrupt normal sperm development and decrease fertility in male patients. In animal studies, teniposide has caused reduced spermatogenesis and testes weight in males, and absent corpora lutea and reduced ovary weight in females.[15]

***Pregnancy:*** FDA Pregnancy Category D.[3,6] There is positive evidence of human fetal risk, 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). In rats, teniposide is embryotoxic and teratogenic. Studies in pregnant women have not been conducted.[1]

***Breastfeeding*** is not recommended due to the potential secretion into breast milk.[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.[16,17]

| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| blood and lymphatic system/ febrile neutropenia | ***anemia*** (88%)[2] |
| | ***leucopenia*** (65-89%)[2,9]; nadir 7-14 days, recovery 14-21 days |
| | ***neutropenia*** (95%) |
| | ***thrombocytopenia*** (80-85%)[2,9]; nadir 7-14 days, recovery 14-21 days |
| cardiac | arrhythmia (1%)[3] |
| gastrointestinal | *emetogenic potential:* low[4,18] |
| | diarrhea[2] |

| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| | ***nausea*** (10-30%)[4,18] |
| | ***vomiting*** (10-30%)[4,18] |
| | ***mucositis*** (76%)[3] |
| general disorders and administration site conditions | *extravasation hazard:* irritant[3] |
| | fever (3%)[2] |
| hepatobiliary | hepatic dysfunction (<1%)[2] |
| immune system | ***hypersensitivity reaction*** (1-5%)[2,19]; see paragraph following **Side Effects** table |
| infections and infestations | ***infection*** (12%)[2] |
| metabolism and nutrition | metabolic abnormalities (<1%)[2] |
| musculoskeletal and connective tissue | asthenia |
| neoplasms | leukemia, acute myeloid (5-12%)[5]; latency period 1 year[20] |
| nervous system | headache (1%)[3] |
| renal and urinary | renal dysfunction (<1%)[2] |
| skin and subcutaneous tissue | ***alopecia*** (9%); reversible |
| | rash (3%)[2] |
| | urticaria, with or without pruritus |
| vascular | bleeding (5%)[2] |
| | ***hypotension[13]*** (2%); transient, following rapid IV administration; possibly due to Cremophor EL®[2,18] |

Adapted from standard reference[1] unless specified otherwise.

***Hypersensitivity reactions*** may be due to teniposide or the Cremophor EL® vehicle.[1,2,19] Reactions to teniposide are characterized by chills, fever, tachycardia, bronchospasm, dyspnea, hypotension or hypertension and may be related to repeated exposure and cumulative dose.[1,2] Cremophor EL® may cause hypersensitivity reactions by activating complement C3 in a concentration-dependent mechanism or via histamine release.[19] Hypersensitivity reactions may occur on the first or subsequent doses.[1,2] Minor reactions to Cremophor EL® (i.e., flushing and rash) are reported in 10-40% of patients, while major reactions to Cremophor EL® (i.e., potentially life-threatening) are reported in 1.5-3% of patients.[19] Reactions respond promptly to administration of pressor agents, corticosteroids, antihistamines or volume expanders as appropriate.[1]

***Ethanol*** is contained in the teniposide formulation at a concentration of 42.7%(v/v).[1,6] Alcohol content of the formulation may place patients at higher risk for central nervous system effects including impaired ability to drive and operate machinery. Effects may be additive with depressant effects from antiemetic agents.[6]

## INTERACTIONS:

| AGENT | EFFECT | MECHANISM | MANAGEMENT |
|---|---|---|---|
| carbamazepine[21] | decreased serum concentration and systemic effect of teniposide | induction of CYP 3A4 by carbamazepine, may increase teniposide clearance | avoid concurrent therapy if possible; may require increased teniposide dose |

| AGENT | EFFECT | MECHANISM | MANAGEMENT |
|---|---|---|---|
| disulfiram[22] | development of acute and severe alcohol intolerance | inhibition of aldehyde dehydrogenase by disulfiram, leading to development of toxic metabolites of ethanol | avoid concurrent therapy |
| metronidazole[22] | development of acute and severe alcohol intolerance | inhibition of aldehyde dehydrogenase by metronidazole, leading to development of toxic metabolites of ethanol | avoid concurrent therapy |
| phenobarbital[1,20-22] | decreased serum concentration and systemic effect of teniposide | induction of CYP 3A4 by phenobarbital, may increase teniposide clearance | avoid concurrent therapy if possible; may require increased teniposide dose |
| phenytoin[1,20-22] | decreased serum concentration and systemic effect of teniposide | induction of CYP 3A4 by phenytoin, may increase teniposide clearance | avoid concurrent therapy if possible; may require increased teniposide dose |
| sodium salicylate[1,18] | increase in teniposide as free drug; increased drug effect and toxicity | may displace teniposide from plasma proteins | monitor for teniposide toxicity |
| sulfamethiazole[1,18] | increase in teniposide as free drug; increased drug effect and toxicity | may displace teniposide from plasma proteins | monitor for teniposide toxicity |
| tolbutamide[1,18] | increase in teniposide as free drug; increased drug effect and toxicity | may displace teniposide from plasma proteins | monitor for teniposide toxicity |
| vincristine[1,22] | possibly increased neurotoxic effect of vincristine | unknown | monitor for neurotoxicity |

Teniposide is a major substrate of CYP 3A4.[3,11] Inducers of CYP 3A4 may increase the metabolism of teniposide and decrease the systemic effect of teniposide. Inhibitors of CYP 3A4 may decrease the metabolism of teniposide and increase the systemic effect of teniposide.[3]

Teniposide is a substrate for P-glycoprotein (PgP).[3,12] Inducers of PgP may decrease the serum concentration of teniposide and limit its further distribution to specific cells/tissues/organs where PgP is present in large amounts (i.e., brain, T-lymphocytes, testes, etc.).[3,12] Inhibitors of PgP may increase the serum concentration of teniposide and enhance its further distribution to specific cells/tissues/organs where PgP is present in large amounts.[3,12]

Teniposide is a weak inhibitor of CYP 2C9 and CYP 3A4.[3] Clinical significance is unknown.

Glucosamine-induced resistance to teniposide has been shown *in vitro* in humans.[23] As the clinical effect of this response in humans is unknown, concurrent therapy should be avoided.[23]

## SUPPLY AND STORAGE:

***Injection*:** Bristol-Myers Squibb Canada supplies teniposide as a 50 mg ampoule of nonaqueous solution in a concentration of 10 mg/mL. Inactive ingredients include: benzyl alcohol 150 mg, Cremophor EL 2.5 g, and dehydrated ethanol 42.7%(v/v). 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:***
- Concentrate must be diluted prior to IV infusion.[1]
- To prevent extraction of plasticizer DEHP from container, prepare solutions in non-DEHP containers and administer using non-DEHP administration sets.[1]
- Excessive agitation and prolonged infusions (24 h) may cause precipitation. Do not use solutions that have evidence of precipitation.[1]

***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 | not recommended; may increase risk of hypotensive reactions[1] |
| Intermittent infusion | over 30-60 minutes (use non-DEHP administration sets)[1,3] |
| Continuous infusion | has been given[2]; precipitation has been reported with prolonged infusions (24 h)[1]; (use non-DEHP administration sets) |
| 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.

***Adults*:**

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

| | Cycle Length: | |
|---|---|---|
| Intravenous: | 1 week[1,2] | 50-180 mg/m$^2$ IV for one dose on day 1 |
| | 3 weeks[1,2,18] | 30 mg/m$^2$ IV once daily for 5-10 consecutive days starting on day 1 |
| | 3 weeks[1,2] | 60-100 mg/m$^2$ IV once daily for 3-5 consecutive days starting on day 1<br>(total dose per cycle 300 mg/m$^2$) |
| | 1 week[20] | 250 mg/m$^2$ IV for one dose on day 1 |

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

| | | |
|---|---|---|
| | Cycle Length: | |
| | 3 weeks:[1,5] | 100 mg/m$^2$ IV for one dose on day 1 |
| | n/a[1,2] | 165 mg/m$^2$ IV for one dose two days per week |
| | n/a[7,18] | 165 mg/m$^2$ IV for one dose on days 1, 4, 8 and 11 of alternating consolidation cycles |
| *Concurrent radiation:* | no information found | |
| *Dosage in myelosuppression:* | modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression" | |
| *Dosage in renal failure:* | no adjustment required[24] | |
| *Dosage in hepatic failure:* | no information found | |
| *Dosage in dialysis:* | not removed by hemodialysis or peritoneal dialysis[18,24] | |

***Children:***

| | | |
|---|---|---|
| | Cycle Length: | |
| Intravenous***:*** | n/a[5] | 70-180 mg/m² IV once daily for 3 consecutive days starting on day 1 |
| | n/a[5] | 1000 mg/m² IV for one dose |
| | 1 week[1,3] | 165 mg/m² IV for one dose two days per week |
| | n/a[3,7] | 165 mg/m²/dose days 1 and 2 of weeks 3, 13 and 23 |
| | 1 week[3] | 250 mg/m² for one dose on day 1 |

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