

PRODUCT MONOGRAPH

VUMON*
(teniposide)

Injection, 10 mg

Antineoplastic Agent

Bristol-Myers Squibb Canada
Montreal, Canada

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Control No.: 145466

PRODUCT MONOGRAPH

NAME OF DRUG

VUMON*

(teniposide)

Injection, 10 mg

THERAPEUTIC CLASSIFICATION

Antineoplastic Agent

CAUTION: VUMON (TENIPOSIDE) IS A POTENT DRUG AND SHOULD BE USED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS (SEE WARNINGS AND PRECAUTIONS). BLOOD COUNTS AS WELL AS RENAL AND HEPATIC FUNCTION TESTS MUST BE DONE REGULARLY. DISCONTINUE THE DRUG IF ABNORMAL DEPRESSION OF BONE MARROW OR ABNORMAL RENAL OR HEPATIC FUNCTION IS SEEN.

ACTION AND CLINICAL PHARMACOLOGY

VUMON (teniposide) is a semi-synthetic derivative of podophyllotoxin used in the treatment of neoplastic diseases.

VUMON is a phase-specific cytotoxic drug, acting in the late S₂ or G₂ phase of the cell cycle preventing cells from entering mitosis. VUMON also produces single and double-strand breaks in DNA. The mechanism of action appears to be due to inhibition of type II topoisomerases.

Teniposide produces a dose dependent inhibition of thymidine uptake after 2.5 hours. This however is not accompanied by a comparable reduction in DNA synthesis.

Pharmacokinetics

The pharmacokinetics of teniposide appear to be linear over a range of doses. Drug accumulation does not occur after daily administration for 3 days. No major differences in the disposition of the drug in

adults and children have been identified.

Following intravenous infusion, initial clearance from the central compartment is rapid with a distribution half-life of approximately 1 hour. Teniposide is highly protein bound, >99%. Levels of teniposide in CSF are low relative to simultaneously measured plasma levels. Mean terminal half-life has ranged from approximately 6 to 20 hours with renal clearance accounting for only about 10% of total clearance. While metabolic pathways for teniposide have not been characterized, agents such as phenobarbital and phenytoin that induce hepatic metabolism, have been shown to increase the clearance of teniposide. (See PRECAUTIONS - Drug Interactions.)

INDICATIONS AND CLINICAL USE

VUMON (teniposide) is indicated as follows:

Neuroblastoma

- second-line single agent or combination therapy in patients who have not responded or who have relapsed on other chemotherapeutic regimens.

Non-Hodgkin's Lymphoma

- second-line combination or as a single agent in patients who are or have become refractory to other chemotherapeutic regimens.

Acute Lymphocytic Leukemia

- second-line combination therapy with cytosine arabinoside in patients who have not responded or relapsed on other chemotherapeutic regimens.

CONTRAINDICATIONS

VUMON (teniposide) should not be given to individuals who have demonstrated a previous hypersensitivity to teniposide or to any component of the formulation. Also, it is contraindicated in patients having severe leukopenia, thrombocytopenia and severe hepatic and/or renal impairment.

WARNINGS

Life threatening anaphylactic reactions have occurred following initial teniposide administration or after repeated exposure.

VUMON (teniposide) should be given cautiously to individuals with pre-existing hepatic and/or renal impairment.

Bacterial infection must be brought under control before the administration of VUMON therapy because of the risk of septicemia. Near fatal anaphylactic reactions have occurred following teniposide administration.

Pregnant Women

VUMON may cause fetal harm when administered to a pregnant woman. Embryotoxic and teratogenic effects have been seen in pregnant rats given teniposide. No studies in pregnant women have been conducted. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of child-bearing potential should be advised to avoid becoming pregnant.

Male patients

Preclinical data have demonstrated that teniposide may disrupt normal sperm development and decrease male fertility. For male patients taking Vumon, the preservation of sperm may be considered for the purpose of later fatherhood.

PRECAUTIONS

VUMON (teniposide) should be administered only by individuals experienced with cancer chemotherapeutic drugs. Severe myelosuppression with resultant infection or bleeding may occur. Blood counts as well as renal and hepatic function tests must be done regularly.

VUMON (teniposide) should be administered with care to patients with marrow involvement by tumor and to patients with impaired renal or hepatic function.

Regular monitoring of white blood cell and platelet counts should be performed during treatment with VUMON. If the white blood cell count is below 2000 cells/mm³ or the platelet count is below 75,000 cells/mm³, unless caused by malignant disease, treatment should be postponed until bone marrow recovery is complete.

Care should be taken to ensure that VUMON infusions are given intravenously with indwelling catheter in proper position prior to infusion as extravasation, necrosis and/or thrombophlebitis may result with improper administration.

Instances of hypotension have been reported during VUMON infusion. Therefore, vital signs should be monitored carefully during the first 30-60 minutes after the start of the infusion.

DRUG INTERACTIONS

Anticonvulsants such as phenobarbital and phenytoin increase the clearance rate of teniposide resulting in lower systemic exposure for a given teniposide dose. An increase in dose may be required in patients receiving anticonvulsant therapy.

Tolbutamide, sodium salicylate and sulfamethiazole have been shown *in vitro* to displace teniposide from plasma proteins. Because of extremely high binding of teniposide to proteins, small decreases in binding could result in substantial increases in free drug with associated increased drug effect and toxicity.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The occurrence of acute nonlymphocytic leukemia has been reported in patients treated with VUMON in association with other antineoplastic agents. Teniposide should be considered a potential carcinogen in humans.

Teniposide has been shown to be mutagenic in various bacterial and mammalian genetic toxicity tests. Teniposide has caused gene mutations in murine cell lines and DNA damage in human cell lines. Chromosome aberrations have been demonstrated in several human and murine tissue cultures.

Teniposide has caused reduced spermatogenesis in monkeys and dogs, and reduced testicular and ovarian weights in dogs.

Nursing Women

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VUMON, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics

VUMON contains benzyl alcohol. Benzyl alcohol has been associated with toxicity in newborns. A syndrome characterized by gasping respirations, kernicterus, metabolic acidosis, neurologic deterioration, hematologic abnormalities and death have been reported to occur following administration of benzyl alcohol containing flush solutions to low birth weight, preterm infants.

Acute central nervous system depression, hypotension and metabolic acidosis have been observed in patients who were receiving higher than recommended doses of VUMON, and who were also pre-treated with antiemetic drugs.

ADVERSE REACTIONS

Hematologic

Myelosuppression is often dose-limiting, with leukopenia and thrombocytopenia occurring 7-14 days after VUMON treatment. Sepsis, sometimes fatal, may be a consequence of severe myelosuppression. Bone marrow recovery is usually complete within 2-3 weeks. Leukopenia is more frequent and more severe than thrombocytopenia. Anemia also occurs and immune hemolytic anemia has been reported.

The occurrence of acute nonlymphocytic leukemia has been reported in patients treated with VUMON in association with other antineoplastic agents.

Gastrointestinal

Nausea and vomiting are the major gastrointestinal toxicities. The nausea and vomiting can usually be controlled by antiemetic therapy. Stomatitis/mucositis, anorexia, diarrhea, abdominal pain and hepatic dysfunction may occur.

Alopecia

A high incidence of alopecia has been reported, especially in patients receiving multiple courses of therapy.

Hypotension

Transient hypotension may occur following rapid intravenous administration of VUMON (see Preparation and Administration). Sudden death due to probable arrhythmia and hypotension has been reported.

Hypersensitivity

Anaphylactic-like reactions characterized by chills, fever, tachycardia, bronchospasm, dyspnea, hypotension and rash have been reported to occur during or immediately after VUMON administration.

They may be due to the Cremophor EL[†] component of the vehicle or to teniposide itself. These reactions may occur on the first dose and may occur more commonly in patients with brain tumors or in patients with neuroblastoma. The risk of having a reaction may be related to repeated exposure and cumulative dose. These reactions have usually responded promptly to cessation of the infusion and administration of pressor agents, corticosteroids, antihistamines or volume expanders as appropriate. Flushing, sweating, hypertension and edema have also been reported.

Dermatologic

Urticaria, with or without pruritus has been reported.

Neurotoxicity

Neurotoxicity has been reported, including severe cases of neuropathy in patients due to an interaction of vincristine sulfate and VUMON. Central nervous system depression has been observed in patients receiving higher than recommended doses (see OVERDOSAGE).

Other

The following reactions also have been reported: infection, renal dysfunction hypertension headache, confusion and asthenia.

[†] T.M. of B.A.S.F.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Acute central nervous system depression, hypotension and metabolic acidosis have been observed in patients who were receiving higher than recommended doses of VUMON, and who were also pre-treated with antiemetic drugs.

No proven antidotes have been established for VUMON overdose. The anticipated complications of overdose are secondary to bone marrow suppression.

DOSAGE AND ADMINISTRATION

VUMON is administered after dilution with a suitable parenteral vehicle, by intravenous infusion.

The following TABLE I is given to provide a guideline for dosage schedules in neuroblastoma, non-Hodgkin's lymphoma, and acute lymphocytic leukemia.

To avoid the possibility of hypotensive reactions, VUMON should not be administered by bolus injection or rapid infusion.

The current literature should be consulted for specific doses and regimens for particular indications.

Monotherapy

Total dose per course is 300 mg/m², given over a 3-5 day period. Cycles may be repeated every 3 weeks or upon recovery of bone marrow.

Dosage should be adjusted according to individual patient variability and toxicity, when employed as a single agent or in combination with other antineoplastic agents.

Combination Therapy

VUMON has been used in combination with several other approved chemotherapeutic agents as shown in TABLES II, III and IV. When it is used in combination with other myelosuppressive drugs, the dose should be appropriately reduced.

NOTE: Patients with Down's Syndrome may be especially sensitive to myelosuppressive chemotherapy, therefore, dose modification may need to be considered in these patients.

TABLE I

Indication	VUMON Dose and Schedule
Neuroblastoma	
Single Agent	130 - 180 mg/m ² /day once weekly given in normal saline or 5% dextrose in water intravenously at a concentration of 0.2 mg/mL over a minimum of 30 minutes
Combination	100 mg/m ² /day every 21 days given in normal saline or 5% dextrose in water intravenously at a concentration of 0.2 mg/mL over a minimum of 30 minutes
Non Hodgkin's Lymphoma	
Single Agent	The following regimens have been used: 30 mg/m ² /day for 10 days given in normal saline or 5% dextrose in water intravenously at a concentration of 0.2 mg/mL over a minimum of 30 minutes 30 mg/m ² /day for 5 days given in normal saline or 5% dextrose in water intravenously at a concentration of 0.2 mg/mL over a minimum of 30 minutes 50 - 100 mg/m ² /day once weekly given in normal saline or 5% dextrose in water intravenously at a concentration of 0.2 mg/mL over a minimum of 30 minutes
Combination	60 - 70 mg/m ² /day once weekly given in normal saline or 5% dextrose in water intravenously at a concentration of 0.2 mg/mL over a minimum of 30 minutes
Acute Lymphocytic Leukemia	
Combination	165 mg/m ² /day twice weekly given in normal saline or 5% dextrose in water intravenously at a concentration of 0.2 mg/mL over a minimum of 30 minutes

TABLE II**Neuroblastoma (Journal Articles)**

Investigator	Combination	Dose mg/m²	Days on Treatment	Frequency
Hayes (1981)	Teniposide Cisplatin	100 I.V. 90 I.V.	On day 1 On day 1	Every 21 days Every 21 days

TABLE III

Non-Hodgkin's Lymphoma (Journal Articles)

Investigator	Single Therapy	Dose mg/m²	Days of Treatment	Frequency
Single Therapy				
Broc (1972)	Teniposide	30 I.V.	On days 1 - 5	Repeat every 10 - 15 days
Mathe (1974)	Teniposide	30 I.V.	On days 1 - 10	Repeat every 5 days
		30 I.V.	On day 1	
		50 - 100 I.V.	Once weekly	
Combination				
Missett (1977)	Adriamycin	40 I.V.	On day 1	Repeat every 15 to 21 days
	Teniposide	60 I.V.	On day 2	
	Cyclophosphamide	300 I.M.	On day 3 and 4	
	Prednisone	40 P.O.	On days 3 to 7	
Lawkowitz (1975)	Teniposide	50 I.V.		Twice weekly
Durand (1978)	Prednisone	40	On days 1 - 15	Only one cycle was given
	Vincristine	0.7	On days 1, 8 and 15	
	Cyclophosphamide	400	On days 3, 10 and 17	
	Teniposide	70	On days 5, 12 and 19	

TABLE IV

Treatment Schedule for Patients on Combination Therapy - Literature Reports

Investigator	Combination	Dose mg/m2	Days on Treatment	Frequency
Data on file * (Patient 643296)	Teniposide	200 mg I.V.	Once weekly	For 5 weeks
	Methotrexate	480 mg I.V.	On day 36	1 week rest period
	L-asparaginase	10,000 IU I.V.	On day 37 and 51	
	Methotrexate	400 mg I.V.	On day 50	2 weeks rest period
	Cytosine arabinoside	100 mg I.V.	On day 71	3 weeks rest period
		150 mg I.V.	On day 71	
	Teniposide	200 mg I.V.	On days 1 and 14	Repeat, alternating with MTX/L-asp cycle
	Cytosine arabinoside	200 mg I.V.	On days 1 and 14	
	Methotrexate	450 mg I.V.	On days 28 and 42	
L-asparaginase	10,000 IU I.V.	On days 29 and 43		
Data on file (Patient 372366)	Teniposide	247 I.V.	On days 1 and 2	One cycle was given
	Prednisone	31	On days 2-6 and 23-29	
	Methotrexate	432 I.V.	On days 15 and 36	
	Methotrexate	12 I.T.	On day 36	
	Vincristine	1.5	On day 1	
	Vincristine	1.8	On days 22, 29, 62 & 69	
	Adriamycin	60	On days 23 and 63	
	6-mercaptopurine	185	On days 38, 40 and 42	
	6-mercaptopurine	216	On days 29, 41	

* Patient's response occurred after day 71

TABLE V**Acute Lymphocytic Leukemia - Literature Report**

Investigator	Combination	Dose mg/m2	Days on Treatment	Frequency
Data on file	Teniposide	165 I.V.	Twice weekly	
	Cytosine arabinoside	300 I.V.	Twice weekly	
Data on file	Teniposide	175 I.V.	Twice weekly	
	Cytosine arabinoside	300 I.V.	Twice weekly	
Data on file	Teniposide	300 I.V.	Twice weekly	
	Cytosine arabinoside	500 I.V.	Twice weekly	
Data on file	Teniposide	125 I.V.	Twice weekly	
	Vincristine	1.5	Once weekly	For 2 weeks
	Prednisone	50 mg	Daily	For 14 days
	Cytosine arabinoside	165 I.V.	Once weekly during week 4	
Data on file	Teniposide	150 I.V.	On days 1, 5, 8 & 14	
	Cytosine arabinoside	290 I.V.	On days 1, 5, 8 & 14	
Rivera (1980)	Teniposide	165 I.V.	Twice weekly	For 4 weeks
	Cytosine arabinoside	300 I.V.	Twice weekly	

Preparation of Intravenous Solutions

Note: Hard plastic devices made of ABS (a polymer composed of acrylonitrile, butadiene and styrene) have been reported to decompose when exposed to N,N-dimethylacetamide, one of the solvents present in the VUMON formulation. This effect has not been reported for VUMON itself, or for diluted solutions of VUMON.

In order to prevent extraction of the plasticizer DEHP (di(2-ethylhexyl)phthalate) from polyvinyl chloride (PVC) containers, solutions of VUMON should be prepared in non-DEHP containing large volume parenteral containers such as glass or polyolefin containers. VUMON solutions should be administered with non-DEHP containing administration sets.

Immediately before administration, each 5 mL ampule of VUMON containing 50 mg of teniposide must be diluted with 50, 125, 250 or 500 mL of either 5 percent Dextrose Injection or 0.9 percent Sodium Chloride Injection. Such dilution provides final teniposide concentrations of 1, 0.4, 0.2 and 0.1 mg/mL, respectively. The diluted solution should then be administered by intravenous infusion over a minimum of thirty minutes. To reduce the possibility of hypotensive reactions, **VUMON should not be administered by bolus injection or rapid infusion.** Greatest care should be taken to insure that the catheter tip remains in the vein during administration, to avoid extravasation and possible tissue irritation.

When diluted as recommended above, solutions that contain teniposide 0.1 mg, 0.2 mg, or 0.4 mg/mL, are stable under normal fluorescent lighting for 24 hours in the recommended large volume glass or polyolefin parenteral containers. Refrigeration is not recommended. VUMON solutions prepared at a final teniposide concentration of 1 mg/mL, and stored at room temperature under normal fluorescent lighting are less stable, and should be administered within 4 hours of preparation to reduce the potential for precipitation.

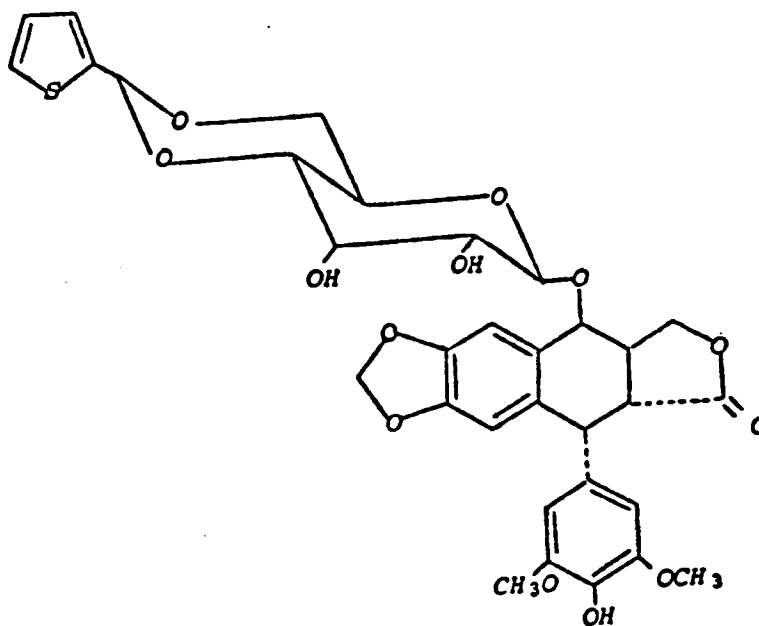
NOTE: This product may precipitate when diluted in any manner, with any diluent or to any concentration other than those described above. If evidence of precipitation does appear, the solution should not be administered. Likewise, precipitation has occurred when prolonged infusions of teniposide (24 hour) were administered through a variety of infusion devices. These infusions, and their delivery systems, should be inspected frequently during administration. Heparin solution can cause precipitation of teniposide, therefore, administration sets/tubing, etc., should be flushed thoroughly with 5% Dextrose Injection or 0.9% Sodium Chloride Injection, before and after administration of VUMON.

Diluted VUMON solutions should be subjected to as little agitation as is necessary to prepare the solution, since excessive agitation can result in precipitation. No other drugs should be mixed with VUMON infusion.

PHARMACEUTICAL INFORMATION

Structural Formula and Chemistry

Teniposide



Molecular Formula: C₃₂H₃₂O₁₃S

Molecular Weight: 656.64

Chemical Name: 4'-demethylepipodophyllotoxin 9-[4,6-O-(R)-2-thenylidene-β-D-glucopyranoside]

Description: Teniposide is very soluble in methanol and chloroform, slightly soluble in ethanol and very slightly soluble in water and ether. It is made water soluble by means of organic solvents.

Handling and Disposal

Caution should be exercised in handling and preparing solutions of VUMON. If VUMON contacts the skin, immediately wash thoroughly with soap and water. If VUMON contacts mucous membranes, flush thoroughly with water.

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in these guidelines are necessary or appropriate.

1. Preparation of VUMON should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II).
2. Personnel preparing VUMON should wear PVC gloves, safety glasses disposable gowns and masks.
3. All needles, syringes, vials and other materials which have come in contact with VUMON should be segregated and incinerated at 1000°C or more. Sealed containers may explode. Intact vials should be returned to the Manufacturer for destruction. Proper precautions should be taken in packaging these materials for transport.
4. Personnel regularly involved in the preparation and handling of VUMON should have bi-annual blood examinations.

Stability

When stored at room temperature (25°C), VUMON packaged in flint glass ampules will remain stable until expiration date indicated on package.

AVAILABILITY OF DOSAGE FORMS

VUMON (teniposide) is supplied in a 5 mL clear glass ampoule containing 50 mg (10 mg/mL) of teniposide dissolved in 5 mL of a nonaqueous solution containing the following: N,N-dimethyl-acetamide 300 mg, benzyl alcohol 150 mg, polyoxyethylated castor oil (Cremophor EL^{††}) 2.5 g, dehydrated ethanol 42.7% (v/v), and maleic acid to adjust pH to approximately 5.

^{††} T.M. of B.A.S.F.

PHARMACOLOGY

In vitro experiments with radio-labelled thymidine have demonstrated that teniposide has a concentration dependent inhibition of thymidine uptake. This however is not accompanied by a comparable reduction in DNA synthesis.

It has been shown that teniposide, in *in vitro* tests on chick connective tissue (fibroblasts), arrested mitosis at metaphase. These effects appeared to be concentration dependent.

Teniposide will inhibit tissue culture *in vitro* as shown in studies with cell line of P-815, KB and L types. The drug has shown activity in rodent transplantable tumors of the sarcomas 37 and 180, TR85, Ehrlich ascites tumor and the Walker carcinosarcoma, as well as leukemias P-815, and L-1210.

In rats, teniposide was distributed in highest concentrations in liver, and adrenal glands thirty minutes after intravenous injection of radio-labelled teniposide. Teniposide accumulated to a significant degree after 24 hours in liver, kidney, large intestine and thyroid.

In monkeys, following oral administration a maximum blood level of teniposide was achieved after 1.5 hours and following an intravenous bolus administration, a maximum level was seen after 15 minutes.

In monkeys, the oral "fast" half life was 1.4 hours, and the intravenous "fast" half life was 1.3 hours, whereas the oral "slow" half life was 10.7 hours, and the intravenous "slow" half life was 6.5 hours. Twenty two percent of the oral dose was excreted in the urine after 80 hours, and 66% of the teniposide oral dose was found in the feces. The urinary excretion of the intravenous dose was 46% and recovery in the feces was 47% after teniposide intravenous dose.

TOXICOLOGY

Acute Toxicity

The LD₅₀ was determined in mice, rats and rabbits (see Table I).

TABLE I

LD₅₀ of teniposide I.V.

		Teniposide solution		Ampoule Solvent
		mg/kg	mL/kg	mL/kg
Mouse	24 hours	26	5.2	4.4
	10 days	16	3.2	4.4
Rat	24 hours	16	3.2	3.7
	10 days	11.3	2.3	3.2
Rabbit	24 hours	7	1.4	1.1
	10 days	7	1.4	1.1

The exact estimate of the toxicity of teniposide is limited by the toxicity of the solvent, so acute intravenous toxicity of teniposide cannot be given with certainty.

Subacute Toxicity

Rats

Teniposide was administered intraperitoneally at doses of 0.6, 1.8 and 6.0 mg/kg/day to three groups of 20 rats (10 males and 10 females) for four weeks.

A dose of 0.6 mg/kg/day produced no significant effects. 1.8 mg/kg/day produced anemia and transient lymphopenia with slight thymus involution and moderately reduced splenic lymphoid tissue. No deaths occurred. 6.0 mg/kg/day had significant effects on the hemopoietic and lymphopoietic systems. Occasional convulsions, hypersensitivity and prolapse of penis were also reported. Non-specific effects (diarrhea, pulmonary lesions, hepatocyte degeneration) were reported. Spermio-genesis and weight gain were slightly impaired in both the 1.8 and 6.0 mg/kg/day groups.

0.6 mg/kg/day produced no significant findings at necropsy. 1.8 mg/kg/day showed slight thymus involution in 10/20 rats, a small quantity of sero-sanguinous ascitic fluid in 4/20 rats, and small petechial hemorrhages in lungs. Swollen and occasionally pale yellow/gray livers were seen. 6.0 mg/kg/day resulted in 14 spontaneous deaths at necropsy. Thymus involution was seen in two rats and sero-sanguinous ascitic fluid was observed in 13/20 rats.

Monkeys

Teniposide was administered intravenously at dosage levels of 0.4, 1.2 and 3.6 mg/kg/day to three groups of two rhesus monkeys (one male and one female) for four weeks.

0.4 mg/kg/day resulted in death in the male and produced diarrhea in the female. 1.2 mg/kg/day produced anemia and leukopenia with an increase in the number of athro-phagocytes in the female. 3.6 mg/kg/day produced severe anemia and leukopenia, agranulocytosis, impaired platelet formation, and hepatocyte degeneration in the female. There was diminished lymphoid tissue and reaction centres in the spleen and lymph nodes in all three groups.

0.4 mg/kg/day at necropsy showed pneumonic infiltrates in the lungs and inflammatory colitis in the male. 1.2 mg/kg/day showed enlarged mesenteric lymph nodes and fatty bone marrow however to a slight degree only. 3.6 mg/kg/day revealed inflammatory colitis in the male and in the female there was evidence of infected gums, dark nodules in the lung, a few petechiae in the bladder mucosa, and the liver and kidney appeared pale.

Chronic Toxicity

Dogs

Three groups of six dogs (3 males and 3 females) were given teniposide intravenously for 26 weeks at 0.1, 0.3 and 1.0 mg/kg on Mondays, Wednesdays and Fridays. Following the completion of the 26 week study, 4 dogs received no drug for an additional eight weeks to detect possible reversibility effects.

At 0.1 mg/kg

There was evidence of slightly impaired food intake and weight gain and increased pH in this group as well as the other two groups (0.3 and 1.0 mg/kg).

At 0.3 mg/kg

Slight relative lymphopenia was observed in one dog as well as mild anemia in one or two dogs.

At 1.0 mg/kg

All six dogs had anemia accompanied by transient reduced reticulocyte counts, increased mean corpuscular volume and mean corpuscular hemoglobin, and slightly increased sedimentation rates. Reduced leukocyte counts were seen with relative lymphopenia occurring in several dogs. Slightly increased platelet counts were seen in several dogs and bone marrow revealed erythropoiesis in most dogs. There were diminished numbers of germinal centres in lymphoid tissue in the spleen and lymph nodes. Extramedullary hemopoiesis was observed in the spleen and liver.

Both 0.3 mg/kg and 1.0 mg/kg produced abnormal nuclear forms in the bone marrow, a slight flattening of T-waves on ECG, impaired spermiogenesis in two males, and an absence of corpora lutea in the ovaries of two females.

At necropsy, the following changes were noted - reduced weight of testes, ovary and spleen; increased liver weights; thymus involution; a malignant lymphoma of the lymphocytic type; degenerative changes in seminal epithelium.

These immunosuppressive effects on the hemopoietic and lymphatic system were reversible following treatment, however, the gonadal effects were still present in one female and one male.

Monkeys

Three groups of six rhesus monkeys (3 males and 3 females) were given teniposide intravenously for 26 weeks at 0.3, 1.0 and 3.0 mg/kg on Mondays, Wednesdays and Fridays. Following the completion of the 26 week study four monkeys, one from each group, were kept for a further 8 weeks without drug administration to demonstrate reversibility of effects.

0.3 mg/kg

Anemia in one monkey and reduced leukocytes were seen.

1.0 mg/kg

Anemia in three to four monkeys, decrease in leukocyte count with relative lymphopenia, variable platelet

count, decreased erythropoiesis and splenic hemopoiesis.

3.0 mg/kg

Anemia associated with a slight increase in mean corpuscular volume and depressed reticulocyte counts was observed. Other hematologic findings showed a decrease in total leukocyte counts with neutropenia, thrombocytosis and quantitative and qualitative changes in bone marrow. There was an increase in SGPT values. Thymus involution was also noted as well as atrophy of lymphoid follicles and lymph nodes, absent spermiogenesis, and increased centrolobular fat in the liver.

The immunosuppressive effects on the hematopoietic and lymphatic system were reversible following withdrawal of treatment, however some bone marrow changes persisted such as a slight decrease in erythropoiesis, increased neutrophil granulation in plasma cells, basophil remnants in the cytoplasm of myelocytes, and metamyelocytes, and karyorrhexis in normoblasts.

In summary, the results of the two 26 week toxicity studies revealed clear-cut toxic effects after intravenous administration of high doses of teniposide in dogs and monkeys. The main evidence of toxicity was seen in the erythro and leukopoietic organs, thymus and testes.

Hemolysis Studies

Teniposide given intravenously to dogs did not appear to produce evidence of intravascular hemolysis. Plasma protein precipitation studies *in vivo* and *in vitro* indicate that intravenous administration of teniposide ampoule solution should have no untoward effect on human blood and plasma at the doses likely to be used.

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