PRODUCT INFORMATION

VUMON®
(Teniposide)

NAME OF THE MEDICINE

VUMON (teniposide, commonly known as VM-26) is a semisynthetic derivative of podophyllotoxin used in the treatment of certain neoplastic diseases.

It is 4’-O-demethyl-1-O(4,6-ß-D-glucopyranosyl) epipodophyllotoxin.

Structural formula:

![Structural formula of teniposide]

Molecular weight 656.7

Molecular formula C_{32}H_{32}O_{13}S

CAS number: 29767-20-2

DESCRIPTION

VUMON a neutral lipophilic compound practically insoluble in water. It must be prepared in organic solvents. VUMON is administered by intravenous infusion.

VUMON Injection is available as a faintly yellow solution in clear glass ampoules containing 50mg of teniposide dissolved in 5mL of an organic solution. Each mL of solution contains 10mg teniposide, 30mg benzyl alcohol, 60mg N,N-dimethylacetamide, 500mg polyoxyethylated castor oil, and ethanol with sufficient maleic acid to give a pH of 5.

PHARMACOLOGY

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

Cells resistant to etoposide were fully cross resistant to teniposide and vice versa in both in vivo and in vitro studies, although there have been occasional clinical reports suggesting a lack of complete cross-resistance.
PHARMACOKINETICS

Absorption
Absorption after oral administration is very variable in man, and teniposide seems to be degraded partially in the gastrointestinal tract. Oral administration is, therefore, not to be recommended.

Distribution
In rats, relatively high concentrations are found in liver, kidneys, adrenals and thyroid and the drug also penetrates into the brain. The volume of distribution in man has been calculated to be \(28.45 \pm 14.5\%\) of body weight.

Protein Binding
Protein binding has been estimated to be approximately 99.4%.

Metabolism
Teniposide is significantly metabolised in the body. Two metabolites have been identified: lignan P, a compound with low toxicity; and a glucuronide.

Excretion
While 30-50% of the administered dose of \(^3\text{H}\)-labelled drug was consistently excreted in the urine, recovery of radioactivity in the faeces varied greatly (from nil to 43%) over 4 days after administration. Unchanged teniposide accounted for 20-28% of the urine radioactivity at 8 hours and for 8-16% at 48 hours post-infusion.

Estimates for plasma clearance and renal clearance of teniposide were \(15.95 \pm 2.50\) mL/min and \(2.22 \pm 0.81\) mL/min respectively.

Half-life
Following a 30 minute infusion of intravenous radiolabelled teniposide (67mg/m\(^2\)) the mean peak plasma level was 14.3 \(\mu\)g/mL, disappearing via a triexponential elimination pattern with a mean terminal half life of 21.2 hours in adults. In children treated with 165mg/m\(^2\), the mean terminal half-life was 9.6 hrs.

Clinical Implications of Pharmacokinetic Data
Teniposide should not be given orally because of erratic absorption from the gastrointestinal tract. Its maximally tolerated dose is approximately one-third that of etoposide, despite similar biochemical actions. This is presumably due to the slower turnover of teniposide in the body and diminished renal clearance.

INDICATIONS
VUMON is indicated in the treatment of:
3. As second-line therapy in non-resectable or recurrent glioma.
4. Advanced transitional cell bladder carcinoma unresponsive to other therapy.
5. As second-line therapy in acute lymphoblastic leukaemia and neuroblastoma in children.

CONTRAINDICATIONS
VUMON is contraindicated in patients who have demonstrated a previous hypersensitivity to teniposide, polyoxyethylated castor oil, or to any component of the formulation.
VUMON is contraindicated in patients who have severe leucopoenia or thrombocytopenia.

**PRECAUTIONS**

VUMON is a potent drug and should be used only by physicians 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. Discontinue the drug if abnormal depression of bone marrow or abnormal renal or hepatic function is seen.

VUMON (teniposide) should be administered with care
(1) to patients with reduced bone marrow reserve;
(2) to patients with impaired renal or hepatic function.

**White Blood Cell and Platelet Count**

Regular monitoring of white blood cell and platelet counts should be performed during treatment with VUMON. If the white blood cell count falls below 2000 cells/mm³ or the platelet count falls below 75,000 cells/mm³, treatment should be suspended until bone marrow recovery is complete (usually after 10 days), as shown by a normal white blood cell and platelet count.

Special care should be taken in patients with impaired medullary haemopoiesis (especially after extensive radiotherapy and/or chemotherapy, or as a result of tumoural infiltration of the bone marrow). The condition may be evidenced by mild to marked leucopoenia and/or thrombocytopenia.

**Administration**

VUMON must not be administered intra-cerebrally, intra-pleurally or intra-peritoneally.

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

**Hypersensitivity**

VUMON Injection contains polyoxyethylated caster oil which has been associated with anaphylactic reactions. The frequency of reactions is substantially higher in patients with neuroblastoma or brain tumours. Life threatening anaphylactic reactions have occurred following initial teniposide administration or after repeated exposure. The anaphylactic reactions consist of flushing of the face and upper thorax, acute respiratory distress with dyspnoea and wheezing, blood pressure changes and tachycardia. Therefore, patients receiving VUMON intravenously should be under continuous observation for at least the first 30 minutes following start of the infusion and at frequent intervals thereafter. If anaphylaxis occurs, the infusion should be discontinued. An aqueous solution of adrenaline 1:1,000 and a source of oxygen should be readily available.

**Impaired Renal and Hepatic Function**

VUMON should be administered with care to patients with impaired renal and hepatic function.

Instances of hypotension have been reported during Vumon infusion. Therefore, vital signs should be monitored carefully during the first 30 to 60 minutes after the start of the infusion.
The occurrence of acute nonlymphocytic leukaemia has been reported in patients treated with Vumon in association with other antineoplastic agents.

Teniposide should be considered a potential carcinogen in humans.

**Bacterial Infections**

Bacterial Infections must be brought under control before treatment with VUMON commences.

**Special Populations**

Patients with Down Syndrome may be especially sensitive to myelosuppressive chemotherapy, therefore dose modifications may need to be considered in these patients.

**Use in Pregnancy**

**Pregnancy Category (Category D)**

VUMON may cause foetal 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. Before 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 foetus. Women of child-bearing potential should be advised to avoid becoming pregnant.

**Use in Lactation**

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 (teniposide), 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.

**Use in Neonates**

Vumon contains benzyl alcohol. Benzyl alcohol has been associated with toxicity in newborns.

A syndrome characterized by gasping respirations, Kernicterus, metabolic acidosis, neurologic deterioration, haematologic abnormalities and death have been reported to occur following administration of benzyl alcohol containing flush solutions to low birth weight, preterm infants.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

VUMON (teniposide) has caused reduced spermatogenesis in monkeys and dogs, and reduced testicular and ovarian weights in dogs.

As teniposide may decrease male fertility, preservation of sperm may be considered for the purpose of later fatherhood.

Chronic toxicity studies in dogs have shown VUMON (teniposide) to have an oncogenic potential.

The occurrence of acute nonlymphocytic leukaemia has been reported in patients treated with
Teniposide 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.

INTERACTIONS WITH OTHER MEDICINES

If radiotherapy or any other cytostatic treatment has been given before starting VUMON treatment, an adequate interval should be allowed to enable the bone marrow to recover. VUMON is clinically compatible with the drugs used in accepted therapeutic protocols, but when used in combination with other myelosuppressive drugs, the dose should be appropriately reduced.

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 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.

ADVERSE EFFECTS

Rapid injection of teniposide results in transient hypotension. This can be minimised by administration of the drug over 30 minutes.

Haematological
The major dose-limiting adverse reaction to teniposide is myelotoxicity. Sepsis, sometimes fatal, may be a consequence of severe myelosuppression. When administered according to the more commonly employed schedules, teniposide monotherapy resulted in leucopenia (less than 5000 white cells/mm³) in 70-100% of cases. The white cell count nadir generally occurs one week after teniposide administration (range 3 days to 2 weeks). Recovery is usually within 2-3 weeks after drug cessation, although it may take longer in patients with poor marrow reserve. Thrombocytopenia is less frequent and almost never occurs without simultaneous leucopenia. Instances of life-threatening or fatal leucopenia and thrombocytopenia have occurred during clinical trials. Anaemia also occurs and immune haemolytic anaemia has been reported.

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

Gastrointestinal
Transient nausea and vomiting are the most commonly reported side effects. They can be controlled by antiemetic drugs. Diarrhoea and loss of appetite are less frequent and abdominal pain occurs rarely. Stomatitis/mucositis, anorexia and hepatic dysfunction may occur.

Urinary Tract
Urinary bladder irritation has been reported only in patients with an infiltrative form of bladder carcinoma.
Alopecia
Reversible alopecia has occurred in up to one-third of patients in clinical trials.

Hypersensitivity
Anaphylactic-like reactions characterised by chills, fever, tachycardia, bronchospasm, dyspnoea, hypotension, and rash have been reported to occur during or immediately after VUMON (teniposide) administration. They may be due to the Cremophor EL^R 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 tumours 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, corticosteroid, antihistamines or volume expanders as appropriate. Flushing, sweating, hypertension and oedema have also been reported.

An antibody to teniposide has been isolated in a patient who suffered acute haemolysis and renal failure during therapy.

Hypotension
Transient hypotension may occur following rapid intravenous administration of teniposide (see PREPARATION AND ADMINISTRATION). Sudden death due to probable arrhythmia and hypotension has been reported.

Dermatological
Transient skin rashes and urticaria, with or without pruritus have been reported.

Neurotoxicity
Neurotoxicity has been reported, including severe cases of neuropathy in patients due to an interaction of vincristine sulphate and VUMON (teniposide). Central nervous system depression has been observed in patients receiving higher than the recommended doses (see OVERDOSE). Peripheral neuropathy and depressed level of consciousness have also been reported.

Other
The following reactions have been rarely reported: stomatitis, headache and confusion, hypertension, infection, renal dysfunction and asthenia. The following reactions have also been reported: sepsis (including fatal cases), mucosal inflammation.

A single case of pulmonary hyaline membrane disease possibly related to teniposide therapy has been reported.

There have been rare cases of reversible elevation in liver transaminases possibly related to teniposide therapy.

DOSAGE AND ADMINISTRATION

All doses are expressed in mg/m^2 body surface area. The drug is given by slow intravenous infusion.

Monotherapy
1. Hodgkin's disease and non-Hodgkin's lymphoma:
The more commonly employed schedules are:
- 30mg/m^2/day for 5 consecutive days with a rest period of 10-14 days between cycles.
- 40-50mg/m^2/day two or three times per week.
- 100mg/m^2 once weekly.
2. Glioma:
100-130 mg/m² once weekly for 6-8 weeks with rest period of 2 weeks between courses.

3. Neuroblastoma and acute leukaemias in children:
100mg/m² twice weekly or 130-180mg/m² once weekly.

4. Transitional cell carcinoma:
30 mg/m² for 5 consecutive days with 10-14 days rest period between cycles.

**Combination Therapy**

VUMON has been used in combination with other approved chemotherapeutic agents. When used in combination with other myelosuppressive drugs, the dose should be appropriately reduced. Peripheral blood counts should be monitored and, if necessary, marrow evaluations performed regularly.

The following drug combinations have been found to be effective:

**Refractory Lymphocytic Leukaemia**

VUMON 165-200mg/m² i.v. with cytarabine 300mg/m² i.v. twice a week for 4 weeks.

**Non-Hodgkin's Lymphoma (NHL)**

The following schedule in which VUMON replaces vincristine without loss of efficacy is associated with no enhanced toxicity and the neurotoxicity associated with vincristine is overcome.

- **VUMON** 100mg/m² i.v. on Day 1
- **Cyclophosphamide** 800mg/m² i.v. on Day 1
- **Prednisone** 60mg/m² p.o. on Day 1-5 then taper off dose over 3 days

Repeat at 3-weekly intervals.

**Hodgkin's Disease and NHL**

An alternate schedule to the above is:

- **VUMON** 40mg/m² i.v. on Days 1 and 2
- **Doxorubicin** 40mg/m² i.v. on Day 2
- **Bleomycin** 15 units i.v. on Days 1 and 2
- **Prednisone** 40mg/m² p.o. on Days 1-8

Cycle repeated every 21 days.

**Brain Tumours**

A combination of:

- **VUMON** 100mg/m² i.v. on Days 1 and 2
- **Lomustine** 60mg/m² p.o. on Days 1 and 2

Repeated every 35 days.
Administration

Note: Hard plastic devices made of ABS (a polymer composed of acrylonitrile, butadine and styrene) have been reported to decompose when exposed to N,N-dimethylacetamide, one of the solvents present in the VUMON formulation.

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.

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

Immediately before administration, each 5mL ampoule of VUMON containing 50mg of teniposide must be diluted with 500 mL of either Sodium Chloride Intravenous Infusion (0.9%) or 5% Glucose Injection. The solution should then be administered by intravenous infusion over a minimum of thirty minutes. To avoid the possibility of hypotensive reactions, VUMON should not be administered by bolus injection or rapid infusion. Greatest care should be taken to ensure that the catheter tip or the needle tip remain in the vein during administration, to avoid extravasation and possible tissue irritation.

Note: To reduce the hazard of microbial contamination, the diluted teniposide should be prepared immediately prior to use and the infusion should be commenced as soon as possible after preparation of the diluted solution.

When diluted as recommended above, solutions contain 0.1 mg teniposide per 1 mL. At this concentration, VUMON solutions are stable for 24 hours in glass large volume parenteral containers. Solutions of VUMON 0.1mg/mL in Sodium Chloride Intravenous Infusion (0.9%) are stable for 8 hours in plastic large volume parenteral containers. VUMON Injection should not be diluted with 5% glucose in plastic bags.

Any unused solution should be discarded after 24 hours (or after 8 hours if dilution occurred in plastic infusion bags containing normal saline). Any storage should be at 2-8°C (Refrigerate - Do not freeze).

Note: The stability of this product when diluted in any manner, with any diluents, or to any concentration other than those described above, may result in the formation of precipitate matter. If evidence of precipitate matter does appear, the solution should be discarded immediately.

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.

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.

Procedures for Handling and Disposal of Anticancer Drugs
Procedures for proper handling and disposal of anticancer drugs should be followed, according to published guidelines.

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.

Care must be taken whenever handling anticancer products. Always take steps to prevent exposure. This includes appropriate equipment, such as, wearing gloves, and washing hands with soap and water after handling such products.

**OVERDOSAGE**

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

The toxicity of VUMON is typically that of a cytostatic drug. Most of the clinical and histopathological findings can be attributed to the cytostatic effect of the drug, haematopoietic tissue being mainly affected. No proven antidotes have been established for VUMON.

In case of overdose, immediately contact the Poisons Information Centre on 13 11 26 for advice.

**PRESENTATION AND STORAGE CONDITIONS**

VUMON Injection. Clear, faintly yellow to yellow solution in clear glass ampoules.

Ampoules each contain 50mg teniposide in 5mL solution. Supplied in packs of 10.

Store below 25 °C. Shelf life: 2 years.

**NAME AND ADDRESS OF THE SPONSOR**

Bristol-Myers Squibb Pharmaceuticals Pty Ltd
556 Princes Highway
Noble Park  Victoria  3174
Australia

**POISON SCHEDULE OF THE MEDICINE**

Prescription Only Medicine (S4)

**Date of first inclusion in the ARTG:** 30 September 1991
**Date of most recent amendment:** 16 April 2012

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