Core Safety Profile

Active substance: Teniposide
Pharmaceutical form(s)/strength: Solution for injection, ampoule, 5ml
P-RMS: AT/H/PSUR/0025/001
Date of FAR: 22.11.2010
4.2 Posology and method of administration

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

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

Immediately before administration, each 5 mL ampule of teniposide 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, teniposide should not be administered by bolus injection or rapid infusion. Greatest care should be taken to ensure 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. TRADEMARK 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 diluents 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 teniposide. Diluted teniposide 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 teniposide infusion.

Combination therapy

Teniposide has been used in combination with several other approved chemotherapeutic agents. When it is 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.

Special populations

Patients with Down syndrome may be especially sensitive to myelosuppressive chemotherapy; therefore, dose modification may need to be considered in these patients.

4.3 Contraindications

Teniposide should not be given to individuals who have demonstrated a previous hypersensitivity to teniposide or to any component of the formulation.
Teniposide is contraindicated in patients who have severe leukopenia or thrombocytopenia.

### 4.4 Special warnings and precautions for use

Teniposide should be used only by physicians experienced with cancer chemotherapeutic drugs.

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

Severe myelosuppression with resultant infection or bleeding may occur. Blood counts as well as renal and hepatic function tests must be done regularly.

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

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 teniposide. 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 teniposide infusions are given through an intravenous catheter in proper position prior to infusion. Extravasation, necrosis and/or thrombophlebitis may result with improper administration.

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

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

Teniposide should be considered a potential carcinogen in humans.

**Pediatric use:** Teniposide 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, 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.

### 4.5 Interaction with other medicinal products and other forms of interaction

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 \textit{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.

4.6 Pregnancy and lactation

Pregnancy

TRADEMARK 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.

Fertility and Contraceptive Measures

Women of child-bearing potential should be advised to avoid becoming pregnant.

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

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 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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, the general condition of the patient being treated should be take into consideration when advice is given relative to driving and/or the operation of dangerous machinery.

4.8 Undesirable effects

The list of undesirable effects shown below is presented by system organ class, MedDRA preferred term, and frequency using the following frequency categories: very common (≥1/10), common (≥1/100, < 1/10), uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1000), very rare (<1/10000), and not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>MedDRA Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Not known</td>
<td>Bone marrow failure, leukaemia, anaemia, haemolytic anaemia, leukopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>Not known</td>
<td>Arrhythmia, tachycardia</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Not known</td>
<td>Abdominal pain, diarrhoea, nausea, stomatitis, vomiting</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Not known</td>
<td>Asthenia, chills, mucosal inflammation, oedema, pyrexia, sudden death</td>
</tr>
<tr>
<td>Hepatobiliary Disorders</td>
<td>Not known</td>
<td>Hepatic function abnormal</td>
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<td>--------------------------------</td>
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<td>---------------------------</td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td>Not known</td>
<td>Anaphylactoid reaction, hypersensitivity</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>Not known</td>
<td>Infection, sepsis</td>
</tr>
<tr>
<td>Metabolism System Disorders</td>
<td>Not known</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Not known</td>
<td>Depressed level of consciousness, headache, neuropathy peripheral, neurotoxicity</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Not known</td>
<td>Confusional state</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>Not known</td>
<td>Renal impairment</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>Not known</td>
<td>Bronchospasm, dyspnoea</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Not known</td>
<td>Alopecia, hyperhidrosis, pruritus, urticaria, rash</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>Not known</td>
<td>Flushing, hypertension, hypotension</td>
</tr>
</tbody>
</table>

**Hematologic**

Myelosuppression is often dose-limiting, with leukopenia and thrombocytopenia occurring 7-14 days after teniposide treatment. Bone marrow recovery is usually complete within 2-3 weeks. Leukopenia is more frequent and more severe than thrombocytopenia. Sepsis, sometimes fatal, may be a consequence of severe myelosuppression.

The occurrence of acute nonlymphocytic leukemia has been reported in patients treated with teniposide 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.

**Hypersensitivity**

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

**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 teniposide. Sudden death due to probable arrhythmia and hypotension has been reported.
Neurotoxicity

Neurotoxicity has been reported, including severe cases of neuropathy in patients due to an interaction of vincristine sulfate and teniposide.

4.9 Overdose

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.

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