Core Safety Profile

Active substance: Etoposide
Pharmaceutical form(s)/strength: oral and injection, phosphate: injection
P-RMS: DK/H/PSUR/0029/001
Date of FAR: 30.06.2012
4.2 Posology and method of administration

TRADEMARKs 1 and 2 Injection
TRADEMARK is administered by slow intravenous infusion. TRADEMARK SHOULD NOT BE GIVEN BY RAPID INTRAVENOUS INJECTION.

Administration Precautions: Hypotension following rapid intravenous administration has been reported. Hence it is recommended that the TRADEMARK solution be administered over a 30- to 60-minute period. Longer infusion times may be required based on patient tolerance. As with other potentially toxic compounds, caution should be exercised in handling and preparing the solution of TRADEMARK. Skin reactions associated with accidental exposure to TRADEMARK may occur. The use of gloves is recommended. If TRADEMARK solution contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

TRADEMARK 1 Oral
The bioavailability of TRADEMARK capsules varies from patient to patient following any oral dose. This should be taken into consideration when prescribing this medication. In view of significant intra-patient variability, dose adjustment may be required to achieve the desired therapeutic effect.

Daily doses greater than 200 mg should be given divided (BID).
Capsules should be taken on an empty stomach.

Dose adjustments:
Dosage of TRADEMARKs 1 and 2 should be modified to take into account the myelosuppressive effects of other drugs in the combination or the effects of prior X-ray therapy or chemotherapy which may have compromised bone marrow reserve.
Patients should not begin a new cycle of treatment with TRADEMARK 1 or 2 if the neutrophil count is less than 1,500 cells/mm³ or the platelet count is less than 100,000 cells/mm³, unless caused by malignant disease.

Doses subsequent to the initial dose should be adjusted if neutrophil count less than 500 cells/mm³ occurs for more than 5 days or is associated with fever or infection, if platelet count less than 25,000 cells/mm³ occurs, if any other grade 3 or 4 toxicity develops or if renal clearance is less than 50 ml/min.
Renal impairment
In patients with impaired renal function, the following initial dose modification should be considered based on measured creatinine clearance.

<table>
<thead>
<tr>
<th>Measured Creatinine Clearance</th>
<th>Dose of Etoposide Phosphate</th>
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</thead>
<tbody>
<tr>
<td>&gt;50 mL/min</td>
<td>100% of dose</td>
</tr>
<tr>
<td>15-50 mL/min</td>
<td>75% of dose</td>
</tr>
</tbody>
</table>

Subsequent dosing should be based on patient tolerance and clinical effect. Data are not available in patients with creatinine clearance <15 mL/min and further dose reductions should be considered in these patients.

4.3 Contraindications
TRADEMARKS 1 and 2 are contraindicated in patients who have demonstrated previous hypersensitivity to etoposide or any component of its formulations.

Concomitant use of yellow fever vaccine or other live vaccines is contraindicated in immunosuppressed patients (see 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use
TRADEMARKs 1 and 2 should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Injection site reactions may occur during the administration of TRADEMARK 1 or 2. Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration. A specific treatment for extravasation reactions is unknown at this time.

Severe myelosuppression with resulting infection or bleeding may occur.

Fatal myelosuppression has been reported following etoposide administration. Patients being treated with TRADEMARKs 1 or 2 must be observed for myelosuppression carefully and frequently both during and after therapy. Dose limiting bone marrow suppression is the most significant toxicity associated with TRADEMARKs 1 and 2 therapy. The following studies should be obtained at the start of therapy and prior to each subsequent dose of TRADEMARK 1 and 2: platelet count, hemoglobin, white blood cell count and differential. If radiotherapy or chemotherapy has been given prior to starting etoposide treatment, an adequate interval should be allowed to enable the bone marrow to recover.
TRADEMARK should not be administered to patients with neutrophil counts less than 1,500 cell/mm³ or platelet counts less than 100,000 cells/mm³, unless caused by malignant disease.

Doses subsequent to the initial dose should be adjusted if neutrophil count less than 500 cells/mm³ occurs for more than 5 days or is associated with fever or infection, if platelet count less than 25,000 cells/mm³ occurs, if any other grade 3 or 4 toxicity develops or if renal clearance is less than 50 ml/min. Dosage should be modified to take into account the myelosuppressive effects of other drugs in the combination or the effects of prior radiation therapy or chemotherapy which may have compromised bone marrow reserve.

The occurrence of acute leukaemia, which can occur with or without myelodysplastic syndrome, has been described in patients that were treated with etoposide containing chemotherapeutic regimens.
Neither the cumulative risk, nor the predisposing factors related to the development of secondary leukaemia are known. The roles of both administration schedules and cumulative doses of etoposide have been suggested, but have not been clearly defined.

An 11q23 chromosome abnormality has been observed in some cases of secondary leukaemia in patients who have received epipodophyllotoxins. This abnormality has also been seen in patients developing secondary leukaemia after being treated with chemotherapy regimens not containing epipodophyllotoxins and in leukaemia occurring de novo. Another characteristic that has been associated with secondary leukaemia in patients who have received epipodophyllotoxins appears to be a short latency period, with average median time to development of leukaemia being approximately 32 months.

Physicians should be aware of the possible occurrence of an anaphylactic reaction with TRADEMARKS 1 and 2, manifested by chills, fever, tachycardia, bronchospasm, dyspnea and hypotension, which can be fatal. Treatment is symptomatic. The infusion should be terminated immediately, followed by the administration of pressor agents, corticosteroids, antihistamines, or volume expanders at the discretion of the physician.

TRADEMARKs 1 and 2 Injection should be given only by slow intravenous infusion (usually over a 30 to 60 minute period) since hypotension has been reported as a possible side effect of rapid intravenous injection.
In all instances where the use of TRADEMARK 1 and 2 is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risk of adverse reactions. Most such adverse reactions are reversible if detected early. If severe reactions occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken according to the clinical judgment of the physician. Reinstitution of TRADEMARK 1 and 2 therapy should be carried out with caution, and with adequate consideration of the further need for the drug and close attention to possible recurrence of toxicity.

Patients with low serum albumin may be at increased risk for etoposide-associated toxicities. Patients with impaired hepatic and renal function should regularly have their renal and hepatic function monitored due to the risk of accumulation.

Bacterial infections should be brought under control before treatment with TRADEMARKs 1 or 2.

Given the mutagenic potential of etoposide, an effective contraception is required for both male and female patients during treatment and up to 6 months after ending treatment. Genetic consultation is recommended if the patient wishes to have children after ending the treatment. As etoposide may decrease male fertility, preservation of sperm may be considered for the purpose of later fatherhood (see 4.6 Pregnancy and lactation).

**Pediatric use**

Safety and effectiveness of TRADEMARKS 1 and 2 in pediatric patients have not been systematically studied.

**TRADEMARK 1 Injection** contains polysorbate 80. In premature infants a life threatening syndrome of liver and renal failure, pulmonary deterioration, thrombocytopenia and ascites has been associated with an injectable vitamin E product containing polysorbate 80.

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

**TRADEMARKS 1 and 2**

High dose cyclosporine, resulting in concentrations above 2000 ng/mL, administered with oral etoposide has led to an 80% increase in etoposide exposure (AUC) with a 38% decrease in total body clearance of etoposide compared to etoposide alone. Concomitant cisplatin therapy is associated with reduced total body clearance of etoposide.
Concomitant phenytoin therapy is associated with increased etoposide clearance and reduced efficacy.
Concomitant warfarin therapy may result in elevated international normalized ratio (INR). Close monitoring of INR is recommended.
There is increased risk of fatal systemic vaccinal disease with the use of yellow fever vaccine. Live vaccines are contraindicated in immunosuppressed patients. (See 4.3 Contraindications.)
Prior or concurrent use of other drugs with similar myelosuppressant action as etoposide/etoposide phosphate may be expected to have additive or synergetic effects (see 4.4 Special warnings and precautions for use).
In vitro plasma protein binding is 97%. Phenylbutazone, sodium salicylate, and aspirin may displace etoposide from plasma protein binding.
Cross resistance between anthracyclines and etoposide has been reported in preclinical experiments.

**TRADEMARK 2**
Caution should be exercised when administering TRADEMARK 2 with drugs that are known to inhibit phosphatase activities.

### 4.6 Pregnancy and lactation
**TRADEMARKs 1 and 2** can cause fetal harm when administered to pregnant women. **TRADEMARK 1 and 2** have been shown to be teratogenic in mice and rats. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant. If these drugs are used during pregnancy, or if the patient becomes pregnant while receiving these drugs, the patient should be apprised of the potential hazard to the fetus.

Given the mutagenic potential of etoposide, an effective contraception is required for both male and female patients during treatment and up to 6 months after ending treatment. Genetic consultation is recommended if the patient wishes to have children after ending the treatment. As etoposide may decrease male fertility, preservation of sperm may be considered for the purpose of later fatherhood.

It is not known whether these drugs are 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 **TRADEMARK 1 and 2**, 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 with TRADEMARKS 1 and 2. If the patient experiences side effects such as fatigue and somnolence they should avoid driving or operating machines.

**4.8 Undesirable effects**
The table below lists adverse events presented by system organ class and frequency, which is defined by the following categories: very common (≥1/10), common (≥1/100,<1/10), uncommon (≥1/1,000,<1/100), and rare (≥1/10,000,<1/1,000).

<table>
<thead>
<tr>
<th>ADVERSE DRUG EVENTS REPORTED with TRADEMARK 1 and 2</th>
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<th></th>
</tr>
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<tbody>
<tr>
<td>(MedDRA Terms)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neoplasms Benign and Malignant (including cysts and polyps)</strong></td>
<td>Common</td>
<td>Acute leukaemia</td>
</tr>
<tr>
<td><strong>Blood and the Lymphatic System Disorders</strong>*</td>
<td>Very common</td>
<td>Myelosuppression*, Leukopenia, thrombocytopenia, neutropenia, anemia</td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td>Common</td>
<td>Myocardial infarction, arrhythmia</td>
</tr>
<tr>
<td><strong>Immune System Disorders</strong></td>
<td>Common (injection: Trademarks 1 and 2)</td>
<td>Anaphylactic-type reactions**</td>
</tr>
<tr>
<td></td>
<td>Rare (oral: Trademark 1)</td>
<td>Anaphylactic-type reactions</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>Common</td>
<td>Dizziness</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Neuropathy peripheral</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Seizure*** optic neuritis, cortical blindness transient, neurotoxicities (e.g., somnolence, fatigue)</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td>Common</td>
<td>Transient systolic hypotension following rapid intravenous administration, hypertension</td>
</tr>
</tbody>
</table>

7/10
<table>
<thead>
<tr>
<th>Disorder Category</th>
<th>Frequency</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>Rare</td>
<td>Pulmonary fibrosis, interstitial pneumonitis</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Very common</td>
<td>Abdominal pain, constipation, nausea and vomiting, anorexia</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Mucositis (including stomatitis and esophagitis), diarrhea</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Dysphagia, dysgeusia</td>
</tr>
<tr>
<td>Hepato-biliary Disorders</td>
<td>Very common</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Very common</td>
<td>Alopecia, pigmentation</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Rash, urticaria, pruritus</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Stevens-Johnson syndrome, toxic epidermal necrolysis, radiation recall dermatitis</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Very common</td>
<td>Asthenia, malaise</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Extravasation****, phlebitis</td>
</tr>
</tbody>
</table>

* Myelosuppression with fatal outcome has been reported.
** Anaphylactic-type reactions can be fatal.
*** Seizure is occasionally associated with allergic reactions.
**** Postmarketing complications reported for extravasation included local soft tissue toxicity, swelling, pain, cellulitis, and necrosis including skin necrosis.

In the paragraphs below the incidences of adverse events, given as the mean percent, are derived from studies that utilized single agent TRADEMARK therapy.

**Hematological Toxicity:**

Myelosuppression with fatal outcome has been reported following administration of etoposide. Myelosuppression is most often dose-limiting. Bone marrow recovery is usually complete by day 20, and no cumulative toxicity has been reported. Granulocyte and platelet nadirs tend to occur about 10-14 days after administration of etoposide or etoposide phosphate depending on the way of administration and treatment scheme. Nadirs tend to occur earlier with intravenous administration compared to oral administration.

Leukopenia and severe leukopenia (less than 1,000 cells/mm³) were observed in 60 - 91% and 7 - 17%, respectively, for etoposide/etoposide phosphate. Thrombocytopenia and severe thrombocytopenia (less than 50,000 platelets/mm³) were seen in 28 - 41% and 4 - 20%, respectively.
respectively, for etoposide/etoposide phosphate. Reports of fever and infection were also very common in patients with neutropenia treated with etoposide/etoposide phosphate.

**Gastrointestinal Toxicity:**
Nausea and vomiting are the major gastrointestinal toxicities of TRADEMARKS 1 and 2. The nausea and vomiting can usually be controlled by antiemetic therapy. They have been noted in 31 - 43% of patients given intravenous TRADEMARK 1. Anorexia was seen in 10 - 13% of patients and stomatitis in 1 - 6% of those patients given intravenous TRADEMARK 1. Diarrhea was noted in 1 - 13% of these patients.

**Alopecia:**
Reversible alopecia, sometimes progressing to total baldness, has been observed in up to 66% of patients treated with TRADEMARK 1 and 44% of patients treated with TRADEMARK 2.

**Blood Pressure Changes**

**Hypotension:**
Transient hypotension following rapid intravenous administration has been reported in patients treated with TRADEMARK 1 or 2 and has not been associated with cardiac toxicity or electrocardiographic changes. Hypotension usually responds to cessation of infusion of etoposide and/or other supportive therapy as appropriate. When restarting the infusion, a slower administration rate should be used. No delayed hypotension has been noted.

**Hypertension:**
In clinical studies involving TRADEMARK 1 and 2, episodes of hypertension have been reported. If clinically significant hypertension occurs in patients receiving TRADEMARK 1 or 2, appropriate supportive therapy should be initiated.

**Allergic Reactions:**
Anaphylactic-type reactions have also been reported to occur during or immediately after intravenous administration of TRADEMARK 1 or 2. The role that concentration or rate of infusion plays in the development of anaphylactic-type reactions is uncertain. Blood pressure usually normalizes within a few hours after cessation of the infusion. Anaphylactic-type reactions can occur with the initial dose of TRADEMARK 1 and 2.
Acute fatal reactions associated with bronchospasm have been reported with TRADEMARK 1 and 2. Facial flushing was reported in 2% of patients and skin rashes in 3% treated with TRADEMARK 2.

**Metabolic Complications:**
Tumour lysis syndrome (sometimes fatal) has been reported following the use of TRADEMARK 1 or 2 in association with other chemotherapeutic drugs.

**4.9 Overdose**

**TRADEMARKS 1 and 2**
Total doses of 2.4 g/m² to 3.5 g/m² administered intravenously over three days have resulted in severe mucositis and myelotoxicity.

Metabolic acidosis and cases of serious hepatic toxicity have been reported in patients receiving higher than recommended intravenous doses of etoposide.

A specific antidote is not available. Treatment should therefore be symptomatic and supportive, and patients should be closely monitored.