# הודעה על החמרה (מידע בטיחות) בעלון לרופא
(מעודכן 3102.50)

**תאריך __October 21, 2014 __**

**שם תכשיר באנגלית ומספר הרישום**

**ETOPOSIDE Concentrate for Solution for Infusion**
**106 48 28897 05**

**שם בעל הרישום Salomon, Levin, & Elstein Ltd.; POBox 3696, Petach Tikva 49133**

טופס זה מיועד לפרוט ההחמרות בלבד !

**ההחמרות המבוקשות**

| טקסט חדש | טקסט נוכחי | פרק בעלון |
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| | | **Indication** |
| Severe myelosuppression, unless when this is caused by the underlying disease.<br>Severe hepatic ~~Liver impairment~~.<br>Hypersensitivity to etoposide or one of the other constituents.<br>Breastfeeding (see section 4.6)<br>Concomitant use of yellow fever vaccine or other live vaccines is contraindicated in immunosuppressed patients (see section "Interaction with other medicinal products and other forms of interaction")<br>~~Patients with severe renal impairment (creatinine clearance < 15 ml/min)~~ | Severe myelosuppression, unless when this is caused by the underlying disease.<br>Liver impairment.<br>Hypersensitivity to etoposide or one of the other constituents.<br>Breastfeeding<br>Patients with severe renal impairment (creatinine clearance < 15 ml/min) | **Contraindications** |
| Dosage of etoposide 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.<br><br>Etoposide is administered by slow intravenous infusion. ETOPOSIDE SHOULD NOT BE ADMINISTERED BY RAPID INTRAVENOUS INJECTION.<br>Hypotension following rapid intravenous administration of etoposide has been reported. Therefore, it is recommended that the etoposide injection be administered by slow i. v. infusion 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 etoposide. Skin reactions associated with accidental exposure to etoposide may occur. The use of gloves is recommended. If etoposide solution contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water. ~~or longer if it is not tolerated. Generally 3 or 4 treatment cycles are carried out.~~<br><br>Patients should not begin a new cycle of treatment with etoposide 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. | ETOPOSIDE SHOULD NOT BE ADMINISTERED BY RAPID INTRAVENOUS INJECTION.<br>Hypotension following rapid intravenous administration of etoposide has been reported. Therefore, it is recommended that the etoposide injection be administered by slow i. v. infusion over a 30 to 60-minute period or longer if it is not tolerated.<br>Generally 3 or 4 treatment cycles are carried out. | **Posology, dosage & administration** |

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| 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.<br><br>*Renal impairment*<br>In patients with impaired renal function, the following initial dose modification should be considered based on measured creatinine clearance.<br><br>**Measured Creatinine Clear ance** / **Dose of Etoposide phosphate**<br>>50 mL/min / 100% of dose<br>15-50 mL/min / 75% of dose<br><br>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. Subsequent etoposide dosing should be based on patient tolerance and clinical effect. | | |
| If etoposide is to be used as part of a chemotherapy regimen, the physician should weigh the necessity to use the drug against the potential risk and side effects (see "Undesirable effects").<br>Etoposide should only be administered under strict observation by a doctor specialized in oncology and use of cancer chemotherapeutic agents, preferable in institutions specialized in such therapies. It should not be injected intraarterially, intrapleurally, or intraperitoneally. Etoposide vials are intended for intravenous administration only. Extravasation should be strictly avoided. 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. ~~If extravasation occurs, the administration should be terminated immediately and restarted in another vein. Cooling, flooding with normal saline and local infiltration with corticosteroids have been reported as therapeutic measures~~<br><br>Fatal myelosuppression has been reported following etoposide administration. Patients being treated with etoposide 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 etoposide therapy. The following studies should be obtained at the start of therapy and prior to each subsequent dose of etoposide: 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.<br>Etoposide should not be administered to patients with neutrophil counts less than 1,500 cell/mm$^3$ or platelet counts less than 100,000 cells/mm3, unless caused by malignant disease. | If etoposide is to be used as part of a chemotherapy regimen, the physician should weigh the necessity to use the drug against the potential risk and side effects (see "Undesirable effects").<br>Etoposide should only be administered under strict observation by a doctor specialized in oncology, preferable in institutions specialized in such therapies. It should not be injected intraarterially, intrapleurally, or intraperitoneally. Etoposide vials are intended for intravenous administration only. Extravasation should be strictly avoided..<br>If extravasation occurs, the administration should be terminated immediately and restarted in another vein. Cooling, flooding with normal saline and local infiltration with corticosteroids have been reported as therapeutic measures<br>If extravasation occurs, the administration should be terminated immediately and restarted in another vein. Cooling, flooding with normal saline and local infiltration with corticosteroids have been reported as therapeutic measures<br><br>One should be aware of the possible occurrence of an anaphylactic reaction manifested by flushing, tachycardia, bronchospasm, and hypotension (see "Undesirable effects" section).<br><br>The substance etoposide can have genotoxic effects. Therefore, men being treated with etoposide are advised not to father a child during and up to 6 months after treatment and to seek advice on | **Special Warnings and Special Precautions for Use** |

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| Doses subsequent to the initial dose should be adjusted if neutrophil count less than 500 cells/mm$^3$ occurs for more than 5 days or is associated with fever or infection, if platelet count less than 25,000 cells/mm$^3$ 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.<br><br>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.<br><br>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.<br><br>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.<br>Physicians should be aware of the possible occurrence of an anaphylactic reaction with etoposide**,** 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<br>~~One should be aware of the possible occurrence of an anaphylactic reaction manifested by flushing, tachycardia, bronchospasm, and hypotension (see "Undesirable effects" section).~~<br><br>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 section "Pregnancy and lactation").<br>~~The substance etoposide can have genotoxic effects. Therefore, men being treated with etoposide are advised not to father a child during and up to 6 months after treatment and to seek advice on cryo-conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with etoposide. Women should not become pregnant during treatment with etoposide.~~<br>In all instances where the use of etoposide is considered | cryo-conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with etoposide. Women should not become pregnant during treatment with etoposide.<br><br>Patients with a low serum albumin concentration may have an increased risk of etoposide toxicity. | |

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| 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.<br>Reinstitution of etoposide 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.<br>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.<br>~~Patients with a low serum albumin concentration may have an increased risk of etoposide toxicity~~.<br><br>The occurrence of acute leukemia, which can occur with or without myelodysplastic syndrome, has been described in patients that were treated with etoposide containing chemotherapeutic regimens.<br>Etoposide injection contain 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<br>This product contains 24% w/v of ethanol. Each 5 ml vial contains up to 1.2 g of alcohol, each 10 ml vial contains up to 2.41 g of alcohol. This can be harmful for those suffering from liver disease, alcoholism, epilepsy, brain injury or disease as well as for children and pregnant women. Alcohol also may modify or increase the effect of other medicines.<br><br>*Pediatric population*<br>Safety and effectiveness of etoposide in pediatric patients have not been systematically studied. | | |
| 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.<br><br>Concomitant cisplatin therapy is associated with reduced total body clearance of etoposide.<br><br>Concomitant phenytoin therapy is associated with increased etoposide clearance and reduced efficacy.<br><br>Concomitant warfarin therapy may result in elevated international normalized ratio (INR). Close monitoring of INR is recommended.<br><br>There is increased risk of fatal systemic vaccinal disease with the use of yellow fever vaccine. Live vaccines are contraindicated in immunosuppressed patients. (See section "Contraindications".)<br><br>Prior or concurrent use of other drugs with similar myelosuppressant action as etoposide/etoposide phosphate may be expected to have additive or | The action of oral anticoagulants can be increased.<br>Phenylbutazone, sodium salicylate and salicylic acid can affect protein binding of etoposide.<br>Etoposide may potentiate the cytotoxic and myelosuppressive action of other drugs.<br>The coadministration of etoposide and high-dose cyclosporine may greatly increase etoposide serum concentrations and risk of adverse reactions. This is probably a result of decreased clearance and increased volume of distribution of etoposide when cyclosporine serum concentration exceeds 2000 ng/mL. The dose of etoposide should be reduced by 50% with concurrent use of high-dose cyclosporine infusion.<br>Co-administration of myelosuppressive drugs (such as cyclophosphamide, BCNU, CCNU, 5-fluorouracil, vinblastine, doxorubicin and cisplatin ) may increase the effect of etoposide | **Interaction with Other Medicaments and Other Forms of Interaction** |

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| synergetic effects (see section "Special warnings and precautions for use").<br><br>*In vitro* plasma protein binding is 97%.<br>Phenylbutazone, sodium salicylate, and aspirin may displace etoposide from plasma protein binding.<br>Cross resistance between anthracyclines and etoposide has been reported in preclinical experiments.<br><br>~~The action of oral anticoagulants can be increased.~~<br>~~Phenylbutazone, sodium salicylate and salicylic acid can affect protein binding of etoposide.~~<br>~~Etoposide may potentiate the cytotoxic and myelosuppressive action of other drugs.~~<br>~~The coadministration of etoposide and high-dose cyclosporine may greatly increase etoposide serum concentrations and risk of adverse reactions. This is probably a result of decreased clearance and increased volume of distribution of etoposide when cyclosporine serum concentration exceeds 2000 ng/mL. The dose of etoposide should be reduced by 50% with concurrent use of high-dose cyclosporine infusion.~~<br>~~Co-administration of myelosuppressive drugs (such as cyclophosphamide, BCNU, CCNU, 5-fluorouracil, vinblastine, doxorubicin and cisplatin ) may increase the effect of etoposide and/or co-administered drug on the bone marrow.~~<br><br>~~Experimentally confirmed cross-resistance between anthracyclines and etoposide has been reported.~~ | and/or co-administered drug on the bone marrow.<br>Experimentally confirmed cross-resistance between anthracyclines and etoposide has been reported. | |
| *Pregnancy and women of child-bearing potential*<br>Etoposide can cause fetal harm when administered to pregnant women. Etoposide have been shown to be teratogenic in mice and rats (see section "preclinical safety data"). 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.<br><br>*Contraception in males and females*<br>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.<br><br>*Breastfeeding*<br>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 etoposide, 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.<br><br>~~*Pregnancy*~~<br>~~There is no experience with the use of etoposide during the first trimester of human pregnancy and very limited~~ | Pregnancy<br>There is no experience with the use of etoposide during the first trimester of human pregnancy and very limited experience (isolated case reports) during the second and third trimester. Etoposide was teratogenic in animals (see section 5.3). On the basis of the results from animal studies and the mechanism of action of the substance, the use of etoposide during pregnancy, in particular during the first trimester, is advised against. In every individual case, the expected advantages of the treatment should be weighed against the possible risk for the embryo/foetus.<br><br>Lactation<br>Etoposide is excreted into human breast milk. Breast feeding is contraindicated during treatment with etoposide. | **Fertility, Pregnancy and Lactation** |

~~experience (isolated case reports) during the second and third trimester. Etoposide was teratogenic in animals (see section 5.3). On the basis of the results from animal studies and the mechanism of action of the substance, the use of etoposide during pregnancy, in particular during the first trimester, is advised against. In every individual case, the expected advantages of the treatment should be weighed against the possible risk for the embryo/foetus.~~

~~*Lactation*~~
~~Etoposide is excreted into human breast milk. Breast feeding is contraindicated during treatment with etoposide.~~

No studies on the effects on the ability to drive and use machines have been performed with etoposide. If the patient experiences side effects such as fatigue and somnolence they should avoid driving or operating machines.
~~Due to the frequent occurrence of nausea and vomiting, driving and operation of machinery should be discouraged.~~

Due to the frequent occurrence of nausea and vomiting, driving and operation of machinery should be discouraged.

**Effects on ability to drive and use machines**

The following frequencies have been used:
Very common (>1/10)
Common (>1/100, <1/10)
Uncommon (>1/1,000, <1/100)
Rare (>1/10,000, <1/1,000)
Very rare (<1/10,000)
not known (cannot be estimated from the available data).

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| *Neoplasms Benign and Malignant (including cysts and polyps)* | Common | Acute leukaemia* |
| | Not known | Acute promyelocytic leukemia** |
| *Blood and the Lymphatic System Disorders** | Very common | Myelosuppression***,leukopenia, thrombocytopenia, neutropenia, anemia |
| *Cardiac Disorders* | Common | Myocardial infarction, arrythmia |
| | Uncommon | Cyanosis |
| *Immune System Disorders* | Common | Anaphylactic-type reactions**** |
| *Nervous System Disorders* | Very common | neurotoxicities (e.g., somnolence, fatigue) |
| | Common | Dizzines |

The following frequencies have been used:
Very common (>1/10)
Common (>1/100, <1/10)
Uncommon (>1/1,000, <1/100)
Rare (>1/10,000, <1/1,000)
Very rare (<1/10,000) including isolated reports

*Neoplasms benign and malignant*
The risk of secondary leukemia among patients with germ-cell tumours after treatment with etoposide is about 1%. This leukemia is characterised with a relatively short latency period (mean 35 months), monocytic or myelomonocytic FAB subtype, chromosomal abnormalities at 11q23 in about 50% and a good response to chemotherapy. A total cumulative dose (etoposide > 2 g/m²) is associated with increased risk. Etoposide is also associated with development of acute promyelocytic leukemia (APL). High doses of etoposide (> 4,000 mg/m²) appear to increase the risk of APL.

*Blood and lymphatic systems disorders*
Very common: The dose limiting toxicity of etoposide is myelosuppression, predominantly leucopenia and thrombocytopenia (leucopenia in 60 - 91%, severe leucopenia [<1000/µl] in 7 to 17%, thrombocytopenia in 28 - 41%, severe thrombocytopenia [< 50,000/µl] in 4 -20% of patients). Anaemia occurs in approx. 40% of patients.

Myelosuppression is dose limiting, with

**Adverse events**

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| | Uncommon | Neuropathy peripheral |
| | Rare | Seizure***** optic neuritis, transient cortical blindness |
| *Vascular Disorders* | Common | Heamorrhage, Transient systolic hypotension following rapid intravenous administration, hypertension |
| *Respiratory, Thoracic and Mediastinal Disorders* | Uncommon | Bronchospasm, coughing, laryngospasm |
| | Rare | Pulmonary fibrosis, interstitial pneumonitis, apnoea |
| *Gastrointestinal Disorders* | Very common | Abdominal pain, constipation, nausea and vomiting, anorexia |
| | Common | Mucositis (including stomatitis and esophagitis), diarrhea |
| | Rare | Dysphagia, dysgeusia |
| *Hepatobiliary Disorders* | Very common | Hepatotoxicity |
| *Skin and Subcutaneous Tissue Disorders* | Very common | Alopecia, pigmentation |
| | Common | Rash, urticaria, pruritus |
| | Rare | Stevens-Johnson syndrome, toxic epidermal necrolysis, radiation recall dermatitis, hand foot syndrome |
| *General Disorders and Administration Site Conditions* | Very common | Asthenia, malaise |
| | Common | Extravasation******, phlebitis, fatigue |

granulocyte nadirs occurring 5 to 15 days after drug administration and platelet nadirs occurring 9 to 16 days after drug administration. Bone marrow recovery is usually complete by day 21, and no cumulative toxicity has been reported.
Fatal cases of myelosuppression have been reported.
Infections have been reported in patients with bone marrow depression.
Common: Haemorrhage (in patients with severe myeolosuppression)

*Immune system disorders*
Common: Anaphylactic-like reactions characterized by fever, flushing, tachycardia, bronchospasm, and hypotension have been reported (incidence 0.7-2%), also apnoea followed by spontaneous recurrence of breathing after withdrawal of etoposide infusion, increase in blood pressure. The reactions can be managed by cessation of the infusion and administration of pressor agents, corticosteroids, antihistamines and/or volume expanders as appropriate.
Anaphylactoid - like reactions may occur after the first intravenous administration of etoposide.
In children receiving dosages higher than recommended, anaphylactoid-like reactions have been reported more frequently.
Erythema, facial and tongue oedema, coughing, sweating, cyanosis, convulsions, laryngospasm and hypertension have also been observed. The blood pressure usually returns to normal within few hours following cessation of therapy.
*Nervous system disorders*
Common: Central nervous system disorders (fatigue, drowsiness) were observed in 0 - 3% of patients.
Uncommon: Peripheral neuropathies were observed in 0.7% of patients.
Rare: Convulsions have been reported, occasionally in association with hypersensitivity reactions. Asthenia has been reported, as well as paresthesiae.

*Eye disorders*
Rare: Reversible loss of vision. Optic neuritis and transient cortical blindness have been reported.

*Cardiac disorders*
Uncommon: Cases of arrhythmia and myocardial infarction have been reported.

*Vascular disorders*
Common: Transient hypotension

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| *Investigations* | Not known | Increase in bilirubin, SGOT and alkaline phosphatases (High dosages) |

* This leukemia is characterised with a relatively short latency period, monocytic or myelomonocytic FAB subtype, chromosomal abnormalities at 11q23 in about 50% and a good response to chemotherapy. A total cumulative dose (etoposide > 2 g/m²) is associated with increased risk (see section "special warnings and precautions for use").

**Etoposide is also associated with development of acute promyelocytic leukemia (APL). High doses of etoposide (> 4,000 mg/m²) appear to increase the risk of APL.

*** 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, celullitis, and necrosis including skin necrosis.

**Description of selected adverse reactions**
In the paragraphs below the incidences of adverse events, given as the mean percent, are derived from studies that utilized single agent etoposide 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, 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

following rapid intravenous administration has been reported in 1% to 2% of patients. It has not been associated with cardiac toxicity or electrocardiographic changes. To prevent this rare occurrence, it is recommended that etoposide be administered by slow intravenous infusion over a 30- to 60-minute period. If hypotension occurs, it usually responds to supportive therapy after cessation of the administration. When restarting the infusion, a slower administration rate should be used.

*Respiratory, thoracic and mediastinal disorders*
Uncommon: Bronchospasm, coughing, cyanosis, laryngospasm.
Rare: Apnoea, interstitial pneumonitis or pulmonary fibrosis.

*Gastrointestinal disorders*
Very common: Nausea and vomiting are the major gastrointestinal toxicities (30-40%). The severity of such nausea and vomiting is generally mild to moderate with treatment discontinuation required in 1% of patients. Anorexia (10-13%).
Common: Abdominal pain and diarrhoea (1-13%) are commonly observed. Stomatitis has been observed in approx. 1 - 6 % of patients
Uncommon: Mucositis and oesophagitis may occur.
Rare: Constipation and swallowing disorders have been observed rarely. Dysphagia and taste impairment have been reported.

*Hepato-biliary disorder*
Common: Hepatic dysfunction has been observed in 0 - 3% of patients. High dosages of etoposide may cause an increase in bilirubin, SGOT and alkaline phosphatases.

*Skin and subcutaneous tissue disorders*
Very common: Reversible alopecia, sometimes progressing to total baldness was observed in up to 70% of patients.
Uncommon: Rash, urticaria, pigmentation and pruritus have also been reported following the administration of etoposide.
Very Rare: toxic epidermal necrolysis (1 fatal case). Stevens Johnson syndrome has also been reported, however, a causal relationship with etoposide has not been established. Radiation "recall" dermatitis, hand-foot syndrome.

*Renal and urinary disorders*
Etoposide has been shown to reach high concentrations in the liver and

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| toxicities of etoposide. The nausea and vomiting can usually be controlled by antiemetic therapy. They have been noted in 31 - 43% of patients given intravenous etoposide. Anorexia was seen in 10 - 13% of patients and stomatitis in 1 - 6% of those patients given intravenous etoposide. Diarrhea was noted in 1 - 13% of these patients.<br><br>*Alopecia:*<br>Reversible alopecia, sometimes progressing to total baldness, has been observed in up to 66% of patients treated with etoposide and 44% of patients treated with etoposide phosphate.<br><br>***Blood Pressure Changes***<br>*Hypotension:*<br>Transient hypotension following rapid intravenous administration has been reported in patients treated with etoposide 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.<br>No delayed hypotension has been noted.<br><br>*Hypertension:*<br>In clinical studies involving etoposide, episodes of hypertension have been reported. If clinically significant hypertension occurs in patients receiving etoposide, appropriate supportive therapy should be initiated.<br><br>*Allergic Reactions:*<br>Anaphylactic-type reactions have also been reported to occur during or immediately after intravenous administration of etoposide. 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.<br>Anaphylactic-type reactions can occur with the initial dose of etoposide.<br>Acute fatal reactions associated with bronchospasm have been reported with etoposide. Facial flushing was reported in 2% of patients and skin rashes in 3% treated with etoposide phosphate.<br><br>*Metabolic Complications:*<br>Tumour lysis syndrome (sometimes fatal) has been reported following the use of etoposide in association with other chemotherapeutic drugs.<br><br>~~The following frequencies have been used:~~<br>~~Very common (>1/10)~~<br>~~Common (>1/100, <1/10)~~<br>~~Uncommon (>1/1,000, <1/100)~~<br>~~Rare (>1/10,000, <1/1,000)~~<br>~~Very rare (≤1/10,000) including isolated reports~~<br><br>~~*Neoplasms benign and malignant*~~<br>~~The risk of secondary leukemia among patients with germ cell tumours after treatment with etoposide is~~ | kidney, thus presenting a potential for accumulation in cases of functional impairment.<br><br>*General disorders and administration site conditions*<br>Etoposide has been shown to reach high concentrations in the liver and kidney, thus presenting a potential for accumulation in cases of functional impairment.<br>Rare: In rare cases, phlebitis has been observed following bolus injection of etoposide.<br>This adverse reaction can be avoided by I.V. infusion over 30 to 60 minutes.<br>After extravasation, irritation of soft tissue and inflammation occur occasionally. Hyperuricaemia due to rapid destruction of malignant cells. | |

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| about 1%. This leukemia is characterised with a relatively short latency period (mean 35 months), monocytic or myelomonocytic FAB subtype, chromosomal abnormalities at 11q23 in about 50% and a good response to chemotherapy. A total cumulative dose (etoposide > 2 g/m²) is associated with increased risk.<br>Etoposide is also associated with development of acute promyelocytic leukemia (APL). High doses of etoposide (> 4,000 mg/m²) appear to increase the risk of APL.<br><br>*Blood and lymphatic systems disorders*<br>Very common: The dose limiting toxicity of etoposide is myelosuppression, predominantly leucopenia and thrombocytopenia (leucopenia in 60 – 91%, severe leucopenia [<1000/µl] in 7 to 17%, thrombocytopenia in 28 – 41%, severe thrombocytopenia [< 50,000/µl] in 4 -20% of patients). Anaemia occurs in approx. 40% of patients.<br><br>Myelosuppression is dose limiting, with granulocyte nadirs occurring 5 to 15 days after drug administration and platelet nadirs occurring 9 to 16 days after drug administration. Bone marrow recovery is usually complete by day 21, and no cumulative toxicity has been reported.<br>Fatal cases of myelosuppression have been reported.<br>Infections have been reported in patients with bone marrow depression.<br>Common: Haemorrhage (in patients with severe myeolosuppression)<br><br>*Immune system disorders*<br>Common: Anaphylactic-like reactions characterized by fever, flushing, tachycardia, bronchospasm, and hypotension have been reported (incidence 0.7-2%), also apnoea followed by spontaneous recurrence of breathing after withdrawal of etoposide infusion, increase in blood pressure. The reactions can be managed by cessation of the infusion and administration of pressor agents, corticosteroids, antihistamines and/or volume expanders as appropriate. Anaphylactoid – like reactions may occur after the first intravenous administration of etoposide.<br>In children receiving dosages higher than recommended, anaphylactoid-like reactions have been reported more frequently.<br>Erythema, facial and tongue oedema, coughing, sweating, cyanosis, convulsions, laryngospasm and hypertension have also been observed. The blood pressure usually returns to normal within few hours following cessation of therapy.<br>*Nervous system disorders*<br>Common: Central nervous system disorders (fatigue, drowsiness) were observed in 0 – 3% of patients.<br>Uncommon: Peripheral neuropathies were observed in 0.7% of patients.<br>Rare: Convulsions have been reported, occasionally in association with hypersensitivity reactions. Asthenia has been reported, as well as paresthesiae.<br><br>*Eye disorders*<br>Rare: Reversible loss of vision. Optic neuritis and transient cortical blindness have been reported. | | |

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| *Cardiac disorders*<br>Uncommon: Cases of arrhythmia and myocardial infarction have been reported.<br><br>*Vascular disorders*<br>Common: Transient hypotension following rapid intravenous administration has been reported in 1% to 2% of patients. It has not been associated with cardiac toxicity or electrocardiographic changes. To prevent this rare occurrence, it is recommended that etoposide be administered by slow intravenous infusion over a 30- to 60-minute period. If hypotension occurs, it usually responds to supportive therapy after cessation of the administration. When restarting the infusion, a slower administration rate should be used.<br><br>*Respiratory, thoracic and mediastinal disorders*<br>Uncommon: Bronchospasm, coughing, cyanosis, laryngospasm.<br>Rare: Apnoea, interstitial pneumonitis or pulmonary fibrosis.<br><br>*Gastrointestinal disorders*<br>Very common: Nausea and vomiting are the major gastrointestinal toxicities (30-40%). The severity of such nausea and vomiting is generally mild to moderate with treatment discontinuation required in 1% of patients. Anorexia (10-13%).<br>Common: Abdominal pain and diarrhoea (1-13%) are commonly observed. Stomatitis has been observed in approx. 1 - 6 % of patients<br>Uncommon: Mucositis and oesophagitis may occur.<br>Rare: Constipation and swallowing disorders have been observed rarely. Dysphagia and taste impairment have been reported.<br><br>*Hepato-biliary disorder*<br>Common: Hepatic dysfunction has been observed in 0 - 3% of patients. High dosages of etoposide may cause an increase in bilirubin, SGOT and alkaline phosphatases.<br><br>*Skin and subcutaneous tissue disorders*<br>Very common: Reversible alopecia, sometimes progressing to total baldness was observed in up to 70% of patients.<br>Uncommon: Rash, urticaria, pigmentation and pruritus have also been reported following the administration of etoposide.<br>Very Rare: toxic epidermal necrolysis (1 fatal case). Stevens-Johnson syndrome has also been reported, however, a causal relationship with etoposide has not been established. Radiation "recall" dermatitis, hand-foot syndrome.<br><br>*Renal and urinary disorders*<br>Etoposide has been shown to reach high concentrations in the liver and kidney, thus presenting a potential for accumulation in cases of functional impairment.<br><br>*General disorders and administration site conditions*<br>Etoposide has been shown to reach high concentrations in the liver and kidney, thus presenting a potential for | | |

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| ~~accumulation in cases of functional impairment.~~<br>~~Rare: In rare cases, phlebitis has been observed following bolus injection of etoposide.~~<br>~~This adverse reaction can be avoided by I.V. infusion over 30 to 60 minutes. After extravasation, irritation of soft tissue and inflammation occur occasionally.~~<br>~~Hyperuricaemia due to rapid destruction of malignant cells.~~ | | |
| A specific antidote is not available. Treatment should therefore be symptomatic and supportive, and patients should be closely monitored. | | **Overdose** |
| | | **Pharmacodynamic properties** |
| | | **Pharmacokinetic properties** |