PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:
P&U ETOPOSIDE CSV 100 mg/5 ml INJECTION
(INJECTION CONCENTRATE FOR INTRAVENOUS INFUSION)

COMPOSITION
Each vial contains 20 mg/ml Etoposide.
Alcohol (100%) 33,16% v/v

CATEGORY AND CLASS
A 26 Cytostatic agents

PHARMACOLOGICAL ACTION
Etoposide is an epipodophyllotoxin. Although the biochemical mechanisms of action are not yet understood, it is cell-cycle dependent and cycle-phase specific. At low concentrations it blocks cells at the S-G2 interface of the cell cycle and at higher concentrations causes G2 arrest. The greatest lethality is seen in the S and G2 phases. Single-strand DNA breaks are observed in intact cells, but not with purified DNA, suggesting that cellular enzymes are in some way involved.

After intravenous administration, peak plasma concentrations of 30 µg/ml are achieved; there is a biphasic pattern of clearance, with a terminal half-life of about 8 hours in patients with normal renal function.

INDICATIONS
Etoposide is primarily used for the treatment of testicular tumours, in combination with bleomycin and cisplatin, and in combination with cisplatin for small-cell carcinoma of the lung. It is also active against non-Hodgkin's lymphomas, acute non-lymphocytic leukemia, carcinoma of the breast and Kaposi's sarcoma associated with acquired immunodeficiency syndrome (AIDS).

CONTRAINDICATIONS
Hypersensitivity to Etoposide and excipients or related agents.
Patients with severe hepatic dysfunction.
Pregnancy and lactation.
Severe myelosuppression (especially after extensive radio and/or chemotherapy or as a result of neoplastic infiltration). This condition may be evidenced by mild to marked leucopenia and/or thrombocytopenia.
Acute infections

Due to the possibility of carcinogenicity and mutagenicity of Etoposide, it should only be used in patients of child bearing age or if the expected benefits outweigh the risks of therapy and adequate contraception is used. The patient should be advised of the potential hazard to the foetus if she becomes pregnant.
Males undergoing treatment with etoposide should use contraceptive measures because of the mutagenic potential of the drug to induce chromosomal damage in spermatozoa.
The safety and effectiveness in children has not been established.

WARNINGS and SPECIAL PRECAUTIONS:
ETOPOSIDE should only be administered by individuals experienced in the administration of etoposide chemotherapy. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

Patients being treated with etoposide must be monitored carefully and frequently for myelosuppression both during and after therapy.
If radiotherapy and/or chemotherapy has been given prior to starting treatment, an adequate interval should be allowed to enable bone marrow to recover and circulating blood elements to return to acceptable levels.
Blood counts including measurement of haemoglobin concentrations or haematocrit, leukocyte and platelet count, should be carried out routinely at the start of therapy and prior to each subsequent dose routinely to help predict the onset of bone marrow depression.

Etoposide may also cause stomatitis which may be associated with considerable discomfort.
Hypotension may occur temporarily with intravenous infusion periods of less than 30 minutes.
Special care is necessary in debilitated patients.
Liver and kidney function should be periodically monitored.
Anaphylactic shock followed by chills, fever, tachycardia, bronchospasm, dyspnoea and hypotension may occur. Etoposide should be discontinued immediately and pressor agents, adrenocorticoids, antihistamines or volume expanders should be used.
Bacterial infections should be brought under control before treatment with Etoposide commences.

In all instances where Etoposide is considered for chemotherapy, the physician must evaluate the need and benefit of the medicine against the risk of adverse reactions. In cases where severe reactions occur, the medicine should be reduced in dosage or discontinued and appropriate corrective measures should be taken according to clinical judgement of the physician.
Re-institution of ETOPOSIDE therapy should be carried out with caution, and with adequate consideration of the further need for the medicine and alertness as to the possible recurrence of toxicity.

Dose limiting bone marrow suppression is the most significant toxic effect associated with etoposide therapy, predominantly manifesting as leucopenia, but also thrombocytopenia and sometimes anaemia.
With leucopenia the nadir of the granulocyte count usually occurs 7 to 14 days after a dose with recovery usually complete by the 20th day. With thrombocytopenia, the nadir of the platelet count occurs 9 - 16 days after administration; recovery is usually complete by the 20th day.

ETOPOSIDE MUST NOT BE ADMINISTERED INTRA-PLEURALLY, INTRA-PERITONEALLY OR INTRA-ARTERIALLY

DOSAGE AND DIRECTIONS FOR USE
FOR INTRAVENOUS USE ONLY
The prescriber should consult the current medical literature when choosing a specific dosage. The dose of Etoposide should be based on the clinical response and appearance or severity of toxicity.
Do not administer the injection undiluted.

Etoposide is given by slow intravenous infusion, over 30 to 60 minutes to avoid hypotension, in sodium chloride (0,9%) or glucose (5%) injection.

Usual doses of 50 to 120 mg per m^2 body surface are given daily for 5 days. Lower doses have been suggested for lung cancer. Alternatively, 100 mg per m^2 has been given on alternate days up to a total of 300 mg per m^2. Courses may be repeated after 3 - 4 weeks if the patient's haematological profile is within acceptable limits.
Dilution of Etoposide can be made with sodium chloride (0,9%) or glucose (5%) injection. Resultant concentrations should not be greater than 0,4 mg/ml since precipitation can occur. Discard any unused portions of the single dose vial after withdrawal of the required dose.
It is recommended that the ETOPOSIDE multidose vial be used within 16 hours after first opening the container.

Care must be taken to avoid extravasation, since severe pain and tissue damage may ensue.
Special precautions should be taken for the safe handling and disposal of Etoposide.
Guidelines for handling antineoplastic agents must be followed. Caution and proper disposal of needles, syringes, containers and unused medication, must be taken.

SIDE EFFECTS

Cardiovascular
There have been reports of cardiotoxicity. Hypotension may occur temporarily with intravenous infusion periods of less than 30 minutes. Etoposide is an irritant or vesicant and produces local irritation; thrombophlebitis may occur at the site of injection. Extravasation may lead to ulceration and necrosis.

Neurotoxicity
Peripheral or central neuropathies have been reported and include transient cortical blindness.

Gastro-intestinal
Nausea and vomiting occurs frequently. Stomatitis, diarrhoea, anorexia, abdominal pain, intestinal ulceration and perforation, oesophagitis and mouth ulcers may occur. Wound healing may be delayed.

Hepatotoxicity
Cases of serious hepatic toxicity have been reported, usually in patients receiving higher than recommended doses of etoposide.

Nephrotoxicity

Other adverse effects include hyperuricaemia and acute renal failure due to uric acid nephropathy which may result from the lysis of large numbers of cells and the breakdown of nucleoproteins; nephro-toxicity may also occur.

Other
Other adverse reactions include alopecia. Reversible alopecia may occur in up to half of all patients.
Use of higher than recommended doses has been associated with metabolic acidosis.

Etoposide is an irritant or vesicant and produces local irritation and thrombophlebitis at the site of injection. Extravasation may lead to ulceration and necrosis.

The following effects have been reported: hypersensitivity or anaphylactoid reactions; fever; rashes; skin and nail pigmentation (may be part of an Addison's syndrome); pruritus; urticaria ; dysphagia; fatigue; somnolence; after-taste; hypertension and/or flushing; hyperphosphataemia and other disturbances of electrolyte balance. An apparent hypersensitivity-associated apnoea has been reported.

Fertility
Etoposide administration may lead to suppression of ovarian and testicular function resulting in amenorrhoea and the inhibition of spermatogenesis. Gynaecomastia has been reported.

Carcinogenicity
Secondary malignancies may develop in patients who have previously undergone successful cancer chemotherapy, particularly where alkylating agents were used. This carcinogenic effect has been linked with the ability of antineoplastic agents to induce mutations and with the effects of prolonged immunosuppression, but it is not possible entirely to separate the effects of chemotherapy from those of radiation and the underlying defects associated with the disease state.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

See "Side effects and Special Precautions". Overdosage of etoposide is accompanied by severe myelosuppression and severe nausea and vomiting. Treatment is symptomatic and supportive.

IDENTIFICATION

A clear, colourless solution free from foreign particles.

PRESENTATION

P&U ETOPOSIDE CSV 100 mg/5 ml INJECTION: Single dose plastic vial containing 20 mg/ml

STORAGE INSTRUCTIONS

Store at or below 25° C. Do not refrigerate.
Protect from light until required for use.
Admixtures must be stored between 2°C - 8°C and used within 24 hours.
KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBERS

P&U ETOPOSIDE CSV 100 mg/5 ml INJECTION: 30/26/0410

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd
85 Bute Lane
Sandton
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DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION

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