Etoposide 20 mg/ml concentrate for solution for infusion

PL 33410/0052 & 0083

UKPAR

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Etoposide 20 mg/ml concentrate for solution for infusion

PL 33410/0052 & 0083

LAY SUMMARY

On 3rd November 2010, the MHRA granted APSLA Limited Marketing Authorisations (licences) for the medicinal product, Etoposide 20 mg/ml concentrate for solution for infusion (PL 33410/0052 and 0083). This is a prescription-only medicine (POM).

Etoposide belongs to a class of drugs known as podophyllotoxin derivatives and it slows or stops the growth of cancer cells. Etoposide is one of the medicines used to treat a variety of cancers. It can be used alone or in combination with other chemotherapeutic agents. This medicine is used for the treatment of testicular cancer, lung cancer and certain cases of leukemia (blood cancer).

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of Etoposide 20 mg/ml concentrate for solution for infusion outweigh the risks; hence Marketing Authorisations have been granted.
Etoposide 20 mg/ml concentrate for solution for infusion

PL 33410/0052 & 0083

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted APSLA Limited Marketing Authorisations for the medicinal product, Etoposide 20 mg/ml concentrate for solution for infusion (PL 33410/0052 and 0083) on 3rd November 2010. The product is a prescription-only medicine (POM).

These are national generic applications for Etoposide 20 mg/ml concentrate for solution for infusion, submitted under Article 10.1 of Directive 2001/83 EC, as amended. The applications refer to the Marketing Authorisation for Vepesid 20 mg/ml Concentrate For Solution For Infusion, 5.0 ml Vial (PL 00125/0184), marketed by Bristol-Myers Pharmaceuticals and authorised on 17th February 1976. The reference product has been authorised in the UK for more than 10 years, thus the period of data exclusivity has expired.

Etoposide ATC Code: L01CB01 is a semi-synthetic derivative of podophyllotoxin, used in the treatment of certain neoplastic diseases. Podophyllotoxins inhibit mitosis by blocking microtubular assembly. Etoposide inhibits cell cycle progression at a pre-mitotic phase (late S and G2). It does not interfere with the synthesis of nucleonic acids.

Etoposide is indicated for the management of:

- testicular tumours in combination with other chemotherapeutic agents
- small cell lung cancer, in combination with other chemotherapeutic agents
- monoblastic leukaemia (AML M5) and acute myelomonoblastic leukaemia (AML M4) when standard therapy has failed (in combination with other chemotherapeutic agents)

The medicinal product is presented as a clear, colourless to pale yellow sterile non-aqueous concentrate for solution for infusion, which must be diluted with specified solutions immediately prior to use. Solutions showing any sign of precipitation should not be used. This medicine is not for self-administration; it will be administered to the patient by a healthcare professional under strict observation by a doctor specialised in oncology.

No new pre-clinical or clinical efficacy studies were conducted, which is acceptable given that these are generic applications cross-referring to a product that has been licensed for over 10 years. Bioequivalence studies are not necessary to support these applications for a parenteral product.

The MHRA considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.
The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. Routine pharmacovigilance activities according to Volume 9A of the rules governing medicinal products in the EU will be undertaken whilst the product is on the market; this is considered satisfactory. The reference product has been in use for many years and the safety profile of the active is well-established. The excipients used in the medicinal product are well-established.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). Etoposide is a well-established active substance that has had widespread clinical use for many years. These were applications for a generic product, which will not be administered at a higher dosage, for a longer duration or for different indications than were previously authorised. There is no reason to conclude that marketing of this product will change the overall use pattern of the existing market.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Etoposide

Nomenclature:

INN: Etoposide

Chemical name: (5R,5aR,8aR,9S)-9-[[4,6-O-[(R)-Ethylidene]b-D-glucopyranosyl]oxy]-5-(4-hydroxy-3, 5-dimethoxyphenyl)-5,8,8a,9-tetrahydroisobenzofuro[5,6-f][1,3]benzodioxol-6(5aH)-one.

Structure:

Molecular formula: C_{29}H_{32}O_{13}

Molecular weight: 588.6 g/mol

CAS No: 33419-42-0

Physical form: A white to almost white, crystalline powder

Solubility: Practically insoluble in water, sparingly soluble in methanol and slightly soluble in alcohol and methylene dichloride

The active substance, etoposide, is the subject of a European Pharmacopoeia (Ph. Eur.) monograph.

All aspects of the manufacture and control of etoposide are supported by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability (CEP). This certificate is accepted as confirmation of the suitability of etoposide for inclusion in this medicinal product, when additional tests are applied as detailed in the active substance specification.

The active substance is stored in appropriate packaging. It is packed into double virgin, food-grade, transparent polythene bags. The inner bag and outer bag are closed individually using white polythene straps and are then placed in stainless steel containers with stainless steel lids. Specifications and Certificates of Analysis for all packaging components used have been provided. The primary, polyethylene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for active substance stored in the proposed commercial packaging. Based on the data, a retest period of 2 years is proposed and is accepted.
MEDICINAL PRODUCT

Description & Composition
The medicinal product is presented in 5ml Type I transparent glass vials as a clear, colourless to pale yellow, sterile, non-aqueous concentrate for solution for infusion. Each vial contains 100 mg of etoposide. Immediately prior to administration, Etoposide 20 mg/ml concentrate for solution for infusion must be diluted with either 5% dextrose in water, or 0.9% sodium chloride solution to give a final concentration of 0.2 to 0.4 mg/ml. At higher concentrations precipitation of etoposide may occur (refer to Section 6.6 of SmPC).

Other ingredients consist of pharmaceutical excipients, namely macrogol 300, polysorbate 80, benzyl alcohol, ethanol and citric acid, anhydrous (for pH adjustment). Appropriate justification for the inclusion of each excipient has been provided. All excipients used comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used and no overages.

Pharmaceutical development
Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The aim was to obtain a medicinal product pharmaceutically equivalent to the innovator product, Vepesid 20 mg/ml Concentrate For Solution For Infusion, 5.0 ml Vial (PL 00125/0184, Bristol-Myers Pharmaceuticals).

Impurity data were provided for the proposed product. The impurity profile was satisfactory.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls were considered appropriate given the nature of the product and the method of manufacture. Process validation studies have been conducted and the results are satisfactory. All validation data were within specification.

Finished product specification
The finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.
**Container Closure System**

The medicinal product is presented in 5ml Type I moulded, transparent, flint glass vials, closed with rubber stoppers and sealed with aluminium flip-off, tear-off seals. The vials are packaged, with the product information leaflet, into cardboard outer cartons. Each carton contains 1 vial or 10 vials, although the MAH has stated that not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all packaging components used have been provided, and are satisfactory. The vials satisfy Directive 2002/72/EC (as amended), and are suitable for contact with parenteral preparations.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years has been set for the unopened vial, which is satisfactory. Storage conditions are ‘Do not freeze. Store in the original package, in order to protect from light’.

From a microbiological point of view, the product should be used immediately after dilution. For full details of shelf-life and storage conditions for the diluted medicinal product, refer to Sections 6.3 and 6.4 of the SmPC. Please also refer to Section 6.6 of the SmPC for information on proper handling and disposal of the product and contaminated materials. Solutions showing any sign of precipitation should not be used.

**Bioequivalence Study**

Bioequivalence studies are not necessary to support these applications for a parenteral product.

**Quality Overall Summary**

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**Product Information**

The approved Summaries of Product Characteristics (SmPCs), Patient Information Leaflets (PILs) and labelling are satisfactory. Mock-ups of the PILs and labelling have been provided. The PIL user testing report has been evaluated and is accepted. It supports the readability of the package leaflet.

**Conclusion**

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Etoposide 20 mg/ml concentrate for solution for infusion from a pharmaceutical point of view.
NON-CLINICAL ASSESSMENT

These abridged applications, submitted under Article 10.1 of Directive 2001/83/EC, as amended, are for Etoposide 20 mg/ml concentrate for solution for infusion, claiming to be a generic medicinal version of Vepesid 20 mg/ml Concentrate For Solution For Infusion, 5.0 ml Vial (Bristol-Myers Pharmaceuticals).

No new pre-clinical data have been supplied with these applications and none are required for applications of this type. A pre-clinical overview has been written by a suitably qualified expert and is satisfactory. The CV of the expert has been supplied.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA).

There are no objections to approval of this product from a pre-clinical point of view.
CLINICAL ASSESSMENT

INDICATIONS

Etoposide is indicated for the management of:

- testicular tumours in combination with other chemotherapeutic agents
- small cell lung cancer, in combination with other chemotherapeutic agents
- monoblastic leukaemia (AML M5) and acute myelomonoblastic leukaemia (AML M4) when standard therapy has failed (in combination with other chemotherapeutic agents)

The proposed indications are not the same as those for the reference product, for which acute myelomonoblastic leukaemia has not been approved, but are identical to the indications stated for another product, Eposin (etoposide 20 mg/ml concentrate for solution for infusion, PL 04946/0018), which has been approved since 1996 via a Mutual Recognition (MR) procedure (NL/H/0120/01/MR). During that MR procedure, advice was sought from the Committee on Safety of Medicines on this matter and the indications were accepted. Eposin was originally submitted as a generic version of the same reference product, i.e. Vepesid, as the current application. The indications are, therefore, accepted.

POSOLOGY AND METHOD OF ADMINISTRATION

Full details concerning the posology are provided in the SmPC. The posology is satisfactory.

TOXICOLOGY

The toxicology of etoposide is well-known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY

The clinical pharmacology of etoposide is well known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for these applications.

Pharmacodynamics

Etoposide is a semi-synthetic derivative of podophyllotoxin, used in the treatment of certain neoplastic diseases. Podophyllotoxins inhibit mitosis by blocking microtubular assembly. Etoposide inhibits cell cycle progression at a pre-mitotic phase (late S and G2). It does not interfere with the synthesis of nucleonic acids.

Pharmacokinetics

On intravenous administration, the disposition of etoposide is best described as a biphasic process with an initial half-life of about 1.5 hours. After distribution, half-life is about 40 hours. The terminal half-life is 6-8 hours.

Following a single intravenous dose, etoposide is excreted in the urine for about 63% and in the faeces for about 31% after 80 hours. Etoposide is cleared by both renal and
non-renal processes i.e. metabolism and biliary excretion. In patients with renal
dysfunction plasma etoposide clearance is decreased.

In adults, the total body clearance of etoposide is correlated with creatinine clearance,
serum albumin concentration and non-renal clearance. In children, elevated serum
ALT levels are associated with reduced drug total body clearance. Prior use of
cisplatin may result in a decrease of etoposide total body clearance.

CLINICAL EFFICACY

No new data are submitted and none are required for this type of application. Efficacy
is reviewed in the clinical overview. The efficacy of etoposide is well-established
from its extensive use in clinical practice.

As this product is a concentrate for aqueous solution for intravenous use containing
the same active substance, and in the same concentration, as the currently authorised
UK reference product, Vepesid 20 mg/ml Concentrate For Solution For Infusion, 5.0
ml Vial (Bristol-Myers Pharmaceuticals), no bioequivalence study is required for
these applications. This is in accordance with the “Guideline on the Investigation of

CLINICAL SAFETY

No new safety data have been submitted and none are required for applications of this
type. No new or unexpected safety concerns arose from these applications. Safety is
reviewed in the clinical overview. The safety profile of etoposide is well-known.

EXPERT REPORT

A satisfactory clinical overview is provided, and has been prepared by an
appropriately qualified expert. The CV of the expert has been supplied. The report
refers to 39 publications up to year 2006 and it is dated June 2007.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)
The approved SmPCs are satisfactory.

Patient Information Leaflet (PIL)
The final PILs are in line with the approved SmPCs and are satisfactory.

Labelling
The labelling is satisfactory.

CONCLUSION

Sufficient clinical information has been submitted to support these applications. The
risk-benefit of the product is considered favourable from a clinical perspective. The
grant of Marketing Authorisations was therefore recommended on medical grounds.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Etoposide 20 mg/ml concentrate for solution for infusion are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-ClinICAL
No new pre-clinical data were submitted and none are required for applications of this type.

EFFICACY
The applicant’s Etoposide 20 mg/ml concentrate for solution for infusion has been demonstrated to be a generic version of the reference product, Vepesid 20 mg/ml Concentrate For Solution For Infusion, 5.0 ml Vial (Bristol-Myers Pharmaceuticals).

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPCs are satisfactory.

The PILs are in line with the SmPCs and are satisfactory. The package leaflets have been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results show that the package leaflets meet the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

Mock-ups of the labelling have been provided. The approved labelling artwork complies with statutory requirements.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s Etoposide 20 mg/ml concentrate for solution for infusion and the reference product, Vepesid 20 mg/ml Concentrate For Solution For Infusion, 5.0 ml Vial (Bristol-Myers Pharmaceuticals), are interchangeable. Extensive clinical experience with etoposide is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit ratio is considered to be positive.
Etoposide 20 mg/ml concentrate for solution for infusion

PL 33410/0052 & 0083

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the marketing authorisation applications on 16th February 2010.

2. Following standard checks and communication with the applicant, the MHRA considered the applications valid on 19th February 2010.

3. Following assessment of the applications, the MHRA requested further information relating to the quality dossier on 26th February 2010, and further information relating to the clinical dossier on 24th March 2010 and 2nd September 2010.

4. The applicant responded to the MHRA’s requests, providing further information for the quality sections on 6th August 2010 and further information for the clinical sections on 6th August 2010 and 22nd October 2010 respectively.

5. The applications were determined on 28th October 2010 and granted on 3rd November 2010.
Etoposide 20 mg/ml concentrate for solution for infusion

PL 33410/0052 & 0083

STEPS TAKEN AFTER AUTHORISATION

Not applicable
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Etoposide 20 mg/ml concentrate for solution for infusion (PL 33410/0052 & 0083) is as follows. The only difference between the individual SmPCs is the PL number:

1 NAME OF THE MEDICINAL PRODUCT
Etoposide 20 mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One 5 ml vial contains 20 mg/ml Etoposide concentrate for solution for infusion
Excipients: Benzyl alcohol 30mg/ml
Ethanol: 30.5%v/v
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Concentrate for solution for infusion.
A clear colourless to pale yellow sterile non-aqueous solution

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Etoposide is indicated for the management of:

- testicular tumours in combination with other chemotherapeutic agents
- small cell lung cancer, in combination with other chemotherapeutic agents
- monoblastic leukaemia (AML M5) and acute myelomonoblastic leukaemia (AML M4) when standard therapy has failed (in combination with other chemotherapeutic agents).

4.2 Posology and method of administration
Etoposide concentrate for solution for infusion 20 mg/ml must be diluted immediately prior to use with either 5% dextrose in water, or 0.9% sodium chloride solution to give a final concentration of 0.2 to 0.4 mg/ml. At higher concentrations precipitation of etoposide may occur.

Etoposide should only be administered under strict observation by a doctor specialised in oncology, preferable in institutions specialised in such therapies

The usual dose of etoposide, in combination with other approved chemotherapeutic agents, ranges from 100-120 mg/m²/day via continuous infusion over 30 minutes for 3-5 days, followed by a resting period of 10-20 days.

Generally 3 to 4 chemotherapy cycles are administered. Dose and amount of cycles should be adjusted to the level of bone marrow suppression and the reaction of the tumour.

In patients with renal function impairment the dose should be adjusted.

Etoposide is intended for intravenous administration only.

To prevent the occurrence of hypotension, the infusion should be given over at least 30 minutes.

15
Dosage adjustment in case of renal function impairment.

In patients with a measured creatinine clearance of greater than 50 ml/minute, no initial dose modification is required. In patients with a measured creatinine clearance of 15-50 ml/minute, 75% of the initial recommended etoposide dose should be administered. For patients with a measured creatinine clearance less than 15 ml/minute treatment with Etoposide is contraindicated (see section 4.3)

4.3 Contraindications

Severe myelosuppression, unless this is caused by the underlying disease.

Liver impairment.

Hypersensitivity to etoposide or one of the other constituents.

Breastfeeding.

Patients with severe renal impairment (creatinine clearance < 15 ml/min).

Etoposide contains 30 mg/ml of benzyl alcohol and must not be given to premature babies or newborn infants.

4.4 Special warnings and precautions for use

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 section 4.8).

Etoposide should only be administered under strict observation by a doctor specialised in oncology, preferable in institutions specialised 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. 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.

Etoposide should be given by slow intravenous infusion over a period of 30-60 minutes; rapid intravenous administration may cause hypotension.

One should be aware of the possible occurrence of an anaphylactic reaction manifested by flushing, tachycardia, bronchospasm, and hypotension (see section 4.8).

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 (see section 4.6.).

The occurrence of a leucopenia with a leucocyte count below 2,000/mm$^3$ is an indication to withhold further therapy until the blood counts have sufficiently recovered (usually after 10 days).

The administration of etoposide should be terminated at the occurrence of thrombocytopenia.

Bacterial infections should be treated before the start of the therapy with etoposide. Great care should be taken on giving etoposide to patients who have, or have been exposed to infection with herpes zoster.

The occurrence of bone marrow depression, caused by radiotherapy or chemotherapy, necessitates a resting period. It is advised not to restart treatment with etoposide until the platelet count has reached at least 100,000/mm$^3$.

Peripheral blood counts and liver function should be monitored.
Patients with a low serum albumin concentration may have an increased risk of etoposide toxicity.

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.

This medicinal product contains 30.5% v/v ethanol. Each 5 ml vial contains up to 1.525 g of ethanol. 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.

4.5 Interaction with other medicinal products and other forms of interaction

The action of oral anticoagulants can be increased.

Phenylbutazone, sodium salicylate and salicylic acid can affect protein binding of etoposide.

Etoposide may potentiate the cytotoxic and myelosuppressive action of other drugs.

The co-administration 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.

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.

Experimentally confirmed cross-resistance between anthracyclines and etoposide has been reported.

The occurrence of acute leukemia, which can occur with or without preleukemic phase has been reported in patients treated with etoposide in association with other anti-neoplastic drugs, e.g. bleomycin, cisplatin, ifosfamide, methotrexate.

4.6 Pregnancy and lactation

Pregnancy

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.

Women of childbearing potential should avoid pregnancy and take effective contraceptive measures during treatment with Etoposide.

Lactation

Etoposide is excreted into human breast milk. Breast feeding is contraindicated during treatment with Etoposide.

Fertility

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.
4.7 Effects on ability to drive and use machines
Due to the frequent occurrence of nausea and vomiting, driving and operation of machinery should be discouraged.

4.8 Undesirable effects
The following frequencies have been used:

- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (<1/10,000), not known (cannot be estimated from the available data)

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 - 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 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 myelosuppression)

Immune system disorders
Common: Anaphylactic-like reactions characterised 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.
Seldom hypersensitivity reactions caused by benzyl alcohol may occur.

**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:* Neurological adverse events (insults), such as strokes, 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 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 gastro-intestinal 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 kidney, thus presenting a potential for accumulation in cases of functional impairment.

General disorders and administration site conditions
Etoposide has been shown to reach high concentrations in the liver and kidney, thus presenting a potential for accumulation in cases of functional impairment.

Rare: In rare cases, phlebitis has been observed following bolus injection of etoposide.

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. Hyperuricaemia due to rapid destruction of malignant cells.

4.9 Overdose
Acute overdosage results in severe forms of normally occurring adverse reactions, in particular leucopenia and thrombopenia.

Severe mucositis and elevated values of serum bilirubin, SGOT and alkaline phosphatase have been reported after administration of high doses of etoposide. Metabolic acidosis and severe hepatic toxicity have been reported after administration of dosages higher than recommended.

The management of bone marrow depression is symptomatic, including antibiotics and transfusions.

If hypersensitivity to etoposide occurs, antihistamines and intravenously administered corticosteroids are appropriate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic classification: podophyllotoxin derivatives

ATC Code: L01CB01

Etoposide is a semisynthetic derivative of podophyllotoxin used in the treatment of certain neoplastic diseases. Podophyllotoxins inhibit mitosis by blocking microtubular assembly. Etoposide inhibits cell cycle progression at a premitotic phase (late S and G2).

It does not interfere with the synthesis of nucleonic acids.

5.2 Pharmacokinetic properties

The concentration of etoposide in blood and organs is low with maximum values in the liver and the kidneys. Protein binding could be as high as 98%.

On intravenous administration, the disposition of etoposide is best described as a biphasic process with an initial half-life of about 1.5 hours. After distribution, half-life is about 40 hours. The terminal half-life is 6-8 hours.

Following a single intravenous dose etoposide is excreted in the urine for about 63% and in the faeces for about 31% after 80 hours.

Etoposide is cleared by both renal and nonrenal processes i.e. metabolism and biliary excretion. In patients with renal dysfunction plasma etoposide clearance is decreased.
In adults, the total body clearance of etoposide is correlated with creatinine clearance, serum albumin concentration and nonrenal clearance. In children, elevated serum ALT levels are associated with reduced drug total body clearance. Prior use of cisplatin may result in a decrease of etoposide total body clearance.

5.3 Preclinical safety data

Etoposide has been shown to be embryotoxic and teratogenic in animal experiments with rats and mice.

There are positive results from in vitro and in vivo test with regard to gene and chromosome mutations induced by etoposide. The results justify the suspicion of a mutagenic effect in humans.

No animal tests with regard to carcinogenicity were performed. Based on the DNA-damaging effect and the mutagenic properties, etoposide is potentially carcinogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Macrogol 300
- Polysorbate 80
- Benzyl alcohol
- Ethanol
- Citric acid, anhydrous (for pH adjustment).

6.2 Incompatibilities

Plastic devices made of acrylic or ABS polymers have been reported to crack when used with undiluted Etoposide 20 mg/ml concentrate for solution for infusion. This effect has not been reported with etoposide after dilution of the concentrate for solution for infusion according to instructions.

6.3 Shelf life

Vial before opening

2 years.

After dilution

Chemical and physical in-use stability of the solution diluted to a concentration of 0.2 mg/ml or 0.4 mg/ml has been demonstrated up to 24 hours at 15 – 25 °C.

From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 12 hours at 15 – 25 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Do not freeze. Store in the original package, in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3

Do not store the diluted product in a refrigerator (2 – 8 °C) as this might cause precipitation.

Solutions showing any sign of precipitation should not be used.
6.5 **Nature and contents of container**

Each vial contains 100 mg of etoposide

5ml Type I moulded transparent flint glass vial with a rubber stopper and sealed with an aluminium flip-off tear-off seal.

Pack sizes: 1 vial or 10 vials

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**

Etoposide should not be used without diluting! Dilute with 0.9% sodium chloride or 5% dextrose. Solutions showing any signs of precipitation should not be used.

For waste-disposal and safety information, guidelines on safe-handling of antineoplastic drugs should be followed. Any contact with the fluid should be avoided. During preparation and reconstitution a strictly aseptic working technique should be used; protective measures should include the use of gloves, mask, safety goggles and protective clothing. Use of a vertical laminar airflow (LAF) hood is recommended.

Gloves should be worn during administration. Waste-disposal procedures should take into account the cytotoxic nature of this substance.

If etoposide contacts skin, mucosae or eyes, immediately wash thoroughly with water. Soap may be used for skin cleansing.

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**MARKETING AUTHORISATION HOLDER**

APSLA Limited
Bayview House
49 North Strand Road
Dublin 3
Ireland

**MARKETING AUTHORISATION NUMBER(S)**

- PL 33410/0052
- PL 33410/0083

**DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

03/11/2010

**DATE OF REVISION OF THE TEXT**

03/11/2010
UKPAR Etoposide 20 mg/ml concentrate for solution for infusion PL 33410/0052 & 0083

PRODUCT INFORMATION LEAFLET

PL 33410/0052

PACKAGE LEAFLET: INFORMATION FOR THE USER
Etoposide 20 mg/ml Concentrate for solution for infusion (Etoposide)

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:
1. What Etoposide is and what it is used for
2. Before Etoposide is given to you
3. How Etoposide is given to you
4. Possible side effects
5. How to store Etoposide
6. Further information

1. WHAT ETOPOSIDE IS AND WHAT IT IS USED FOR

The name of this medicine is Etoposide 20 mg/ml Concentrate for solution for infusion. It contains the active ingredient Etoposide. Etoposide belongs to a type of drugs known as podophyllotoxin derivatives and it slows or stops the growth of cancer cells.

Etoposide is one of the medicines used to treat a variety of cancers. It can be used alone or in combination with other chemotherapeutic agents.

This medicine is used for the treatment of testicular cancer, lung cancer and certain cases of leukaemia (blood cancer).

2. BEFORE ETOPOSIDE IS GIVEN TO YOU

When Etoposide SHOULD NOT be given to you
If the answer is YES to any of these questions, you should probably not receive Etoposide. Please discuss the matter with your doctor immediately. However, your doctor may decide that your treatment with Etoposide is essential.
- are you allergic to etoposide or to one of the other ingredients of this concentrate?
- do you have problems with your liver?
- do you have severe kidney problems?
- do you have problems with the functioning of the bone marrow?
- is the treatment used for a new born baby?

When special care should be taken
If the answer is YES to any of these questions, it is important that you discuss the matter with your doctor BEFORE receiving your first injection.
- are you using other drugs to treat cancer?
- are you receiving, or did you receive in the past, radiation therapy?
- are you suffering from infections?

Tell your doctor about any other treatment you receive for your illness.

Using other medicines:
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. In particular you should tell your doctor if you are taking any of the following:
- anti-coagulants such as warfarin which are used to thin the blood
- the analgesic (pain killing) and fever lowering medicines phenylbutazone, aspirin and aspirin related medicines (sodium salicylate or salicylic acid)
- the immunosuppressant ciclosporin (often given after an organ transplant)

Other drugs used to treat other forms of cancer such as vincristine, doxorubicin and cisplatin.

Etoposide can also have effects on other medicines used to treat cancer. Your doctor will take these effects into account when deciding on your treatment.

Using Etoposide with food and drink.
Etoposide is not affected by food or drink.

Pregnancy and breast-feeding
You should not use Etoposide if you are pregnant. If you are pregnant you should inform your doctor immediately.

Women of child bearing age should take effective contraceptive measures.

You should not breastfeed during treatment with Etoposide.

Fathering children whilst taking Etoposide
Men should not father a child whilst being treated with Etoposide and until 6 months after treatment has finished.

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It is advised for men to consider sperm collection (for cryo-conservation) before treatment with etoposide, because infertility after treatment can occur.

Driving and using machines
This medication can cause nausea and vomiting. Precaution is advised in undertaking actions which require extra alertness, such as the use of machines and driving.

Important information about some of the ingredients of Etoposide
This medicinal product contains approximately 50% ethanol (alcohol), i.e. up to 1.5 g per dose. This is equivalent to 30 ml of beer or 12.5 ml of wine per dose. This may be dangerous for patients suffering from alcoholism and for patients in high-risk groups such as those with liver problems or epilepsy (fits). The amount of alcohol in this product may alter the effects of other medicines.

Etoposide contains 30 mg/ml of benzyl alcohol and must not be given to premature babies or new born babies. It may cause toxic and allergic reactions in infants and children up to 3 years old.

3. HOW ETOPOSIDE IS GIVEN TO YOU

Etoposide concentrate for solution for infusion will always be given to you by a healthcare professional. This medicine will be diluted with 0.9% sodium chloride or 5% dextrose and will be given to you as an infusion (a "drip") into a vein.

How much of the injection will you receive and how often?
- The dose of Etoposide will be individually determined by your doctor. The dose you are given depends on your size; it varies with your surface area. Technically, this is measured in square metres, and is worked out from your height and weight.
- You will receive a treatment cycle consisting of one dose a day during 5 - 7 days, followed by a 10 - 20 days rest.
- The administration will take at least 30 minutes.
- Usually three or four treatment cycles are given, but the duration of the treatment and the number of treatments is determined by the doctor and may vary for each patient.
- Etoposide may be given alone or in combination with other medicines.
- Your condition will be closely monitored during treatment. This routinely involves blood tests and controls of your liver function.
- Your dose may be changed depending on your kidney function.
- If you have any questions about your treatment schedule ask your doctor, pharmacist or nurse.
- If you are given too much Etoposide
  - If you think you have received too much medicine consult your doctor or a nurse.
- If you miss a dose of Etoposide
  - If you have missed a dose of your treatment, consult your doctor or a nurse.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Etoposide can cause side effects, although not everybody gets them.

You should discuss these with your doctor who will explain the risks and benefits of your treatment.

Some of the side effects can be lessened or treated by other medicines or therapy.

Tell your doctor immediately if you notice any of the following:
- unexplained bruising, reddish or purplish patches on the skin, nosebleeds and bleeding (these may be signs of a decrease in the number of blood platelets, these cells in the blood that help the blood to clot)
- infections
- severe allergic reactions such as fever, reddening of the face and neck, often with a sudden, subjective feeling of heat (flushing), rapid heartbeat, abnormal contraction of your lungs which can cause a cough and wheezing, abnormally low blood pressure and stopping of breathing.

The following information is intended for medical or healthcare professionals only:

Cytotoxic

Instructions on how to dilute, administer, store and dispose of Etoposide

Dilution

Etoposide 20 mg/ml concentrate for solution for infusion must be diluted immediately prior to use with either 5% dextrose in water, or 0.9% sodium chloride solution to give a final concentration of 0.2 to 0.4 mg/ml. At higher concentrations precipitation of etoposide may occur.

Administration

The usual dose of etoposide, in combination with other approved chemotherapeutic agents, ranges from 100-120 mg/m²/day via continuous infusion over 30 minutes for 3-5 days, followed by a resting period of 10-20 days. Generally 3 to 4 chemotherapy cycles are administered. Dose and amount of cycles should be adjusted to the level of bone marrow suppression and the reaction of the tumour.

In patients with renal function impairment the dose should be adjusted.

Etoposide is intended for intravenous administration only.
It may be necessary to stop your treatment with Etoposide.

Although not all of these side effects may occur, tell your doctor if they do occur, as they may need medical attention.

The following headings are used to organise the side effects in order of frequency:

- Very common: (may affect more than 1 in 10 users)
- Common: (may affect 1 to 10 users in 100)
- Uncommon: (may affect 1 to 10 users in 1,000)
- Rare: (may affect 1 to 10 users in 10,000)
- Very rare: (may affect 1 user in 10,000)

The side effects could include:

**Very Common side effects**
- you may produce less red blood cells (anaemia) and platelets than normal. This will be monitored by your doctor during your treatment with regular blood tests.
- infections
- nausea
- vomiting
- loss of appetite
- reversible loss of hair (alopecia), sometimes progressing to total baldness
- feeling of tiredness due to anaemia

**Common side effects**
- leukaemia (cancer of the blood) in addition to the cancer that you are being treated for
- bleeding
- allergic (hypersensitive) reactions such as fever, reddening of the face and neck, often with a sudden, subjective feeling of heat (flushing), rapid heartbeat, abnormal contraction of your lungs which can cause a cough and wheezing, abnormally low blood pressure and stopping of breathing
- redness of the skin
- social and tongue swelling
- coughing
- sweating
- bluish discoloration of the skin and mucous membranes
- convulsions (fits)
- spasmodic closure of the voice box (larynx)
- abnormally high blood pressure
- fatigue and drowsiness
- low blood pressure causing dizziness when Etoposide is administered too quickly
- abdominal pain
- diarrhoea
- inflammation of the mucous membranes of the mouth
- problems with your liver including increases in liver blood test values (bilirubin, SGOT and alkaline phosphatases); your doctor will monitor your liver function with blood tests during your treatment

**Uncommon side effects**
- damage to nerves of the hand and feet
- irregular heartbeat
- heart attack
- abnormal contractions in your lungs which can cause a cough and wheezing
- coughing
- spasmodic closure of your throat which makes it difficult to breathe
- inflammation of the mucous membranes
- inflammation of the gullet (oesophagus)
- rash
- hives
- darkening of skin (increase in pigmentation)
- itching

**Rare side effects**
- allergic (hypersensitive) reactions caused by benzyl alcohol
- stroke, occasionally in association with allergic reactions
- a feeling of weakness
- sensations such as burning, prickling, itching, or tingling
- reversible loss of vision
- temporary blindness
- inflammation of an optic nerve
- unusually high concentration of uric acid in the blood (gout)
- inflammation of a vein
when you are receiving the infusion, if it leaks into the surrounding tissues then irritation and swelling may occur around the location of the leakage
- stopping breathing
- inflammation of the tissue in the lungs
- formation of scar tissue in the lungs
- constipation
- difficulty in swallowing
- taste impairment
- Etoposide can accumulate in your liver and kidneys, especially if you have liver or kidney problems

Very rare side effects:
- a potentially life-threatening skin disorder accompanied by severe skin blisters and often sores in the membranes of the mouth, nose, eyes and the anal and genital areas
- inflammatory, itching skin reddening following radiation therapy and subsequent treatment with a rash at the site of previous radiotherapy
- redness and pain of palms of hands and soles of feet

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE ETOPOSIDE

Keep out of the reach and sight of children.
Do not use Etoposide after the expiry date which is stated on the vial and carton after EXP. The expiry date refers to the last day of that month.
Keep the vial in the outer carton, in order to protect from light. Do not refrigerate or freeze.
After dilution the solution should be used immediately. If this is not possible, the diluted solution may be stored at 15 - 25 °C for not more than 12 hours.
Left-over of used solutions should be discarded. Solutions showing any signs of precipitation should not be used.
Avoid unnecessary contact with the fluid. Rinse skin immediately after contact with the solution. Be sure your doctor or nurse removes any syringes or vials for disposal.

6. FURTHER INFORMATION

What Etoposide contains:
- The active substance: Etoposide. Each vial (5ml) contains 100 mg Etoposide
- The other ingredients are: benzylic alcohol, citric acid, ethanol, polysorbate 80 and maerogel 300.

What Etoposide looks like and contents of the pack
Etoposide Concentrate for solution for infusion is a clear to pale yellow solution packaged in clear glass vials containing 5 ml of solution. The vials are packed in a carton containing 1 or 10 vials.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
APSLA Limited, Bayview House, 49 North Strand Road, Dublin 1, Ireland.
Manufacturer:
APC Pharmaceuticals & Chemicals (Europe) Ltd.,
9th Floor, CP House, 97-107 Uxbridge Road, Enfield, London W5 STL
Distributed By:
APC Pharmaceuticals & Chemicals (Europe) Ltd.,
9th Floor, CP House, 97-107 Uxbridge Road, Enfield, London W5 STL

This leaflet was last approved in MM/YYYY.

To prevent the occurrence of hypotension, the infusion should be given over at least 30 minutes.

Storage of the prepared solution
Chemical and physical in-use stability has been demonstrated for 24 hours at 15 - 25 °C.
From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 12 hours at 15 - 25 °C, unless dilution has taken place in controlled and validated aseptic conditions.

Handling and disposal
The normal procedures for proper handling and disposal of anti-tumour medicinal products should be adopted:
- Staff should be trained to reconstitute the medicinal product.
- Staff handling this medicinal product during reconstitution should wear protective clothing including mask, goggles and gloves.
- All items, for administration or cleaning, including gloves, should be placed in high-risk, waste disposal bags for high-temperature incineration.
- Liquid waste may be flushed with large amounts of water.
- Accidental contact with the skin or eyes should be treated immediately with copious amounts of water.
UKPAR Etoposide 20 mg/ml concentrate for solution for infusion
PL 33410/0052 & 0083

PL 33410/0083

PACKAGE LEAFLET: INFORMATION FOR THE USER
Etoposide 20 mg/ml Concentrate for solution for infusion
(Etoposide)

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:
1. WHAT ETOPOSIDE IS AND WHAT IT IS USED FOR
2. BEFORE ETOPOSIDE IS GIVEN TO YOU
3. HOW ETOPOSIDE IS GIVEN TO YOU
4. POSSIBLE SIDE EFFECTS
5. HOW TO STORE ETOPOSIDE
6. FURTHER INFORMATION

1. WHAT ETOPOSIDE IS AND WHAT IT IS USED FOR

The name of this medicine is Etoposide 20 mg/ml Concentrate for solution for infusion. It contains the active ingredient Etoposide.

Etoposide is one of the medicines used to treat a variety of cancers. It can be used alone or in combination with other chemotherapeutic agents.

This concentrate is used to make an infusion for the treatment of testicular cancer, lung cancer and certain cases of leukemia (blood cancer).

2. BEFORE ETOPOSIDE IS GIVEN TO YOU

When Etoposide SHOULD NOT be given to you
If the answer is YES to any of these questions, you should probably not receive Etoposide. Please discuss the matter with your doctor immediately. However, your doctor may decide that your treatment with Etoposide is essential.
- are you allergic to etoposide or to one of the other ingredients of this concentrate?
- do you have problems with your liver?
- do you have severe kidney problems?
- do you have problems with the functioning of the bone marrow?
- is the treatment used for a new born baby?
- are you pregnant or planning to become pregnant (see also "Pregnancy and breastfeeding" below)?
- are you breast feeding?

When your special care should be taken
If the answer is YES to any of these questions, it is important that you discuss the matter with your doctor BEFORE receiving your first injection.
- are you using other drugs to treat cancer?
- are you receiving, or did you receive in the past, radiation therapy?
- are you suffering from infections?

Tell your doctor about any other treatment you receive for your illness.

Using other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. In particular you should tell your doctor if you are taking any of the following:
- anti-coagulants such as warfarin which are used to thin the blood
- the analgesic (pain killing) and fever lowering medicines phenacetin, aspirin and aspirin related medicines (sodium salicylate or salicylic acid)
- the immunosuppressant ciclosporin (often given after an organ transplant)
- other drugs used to treat other forms of cancer such as vinblastine, dacarbazine and cisplatin

Etoposide can also have effects on other medicines used to treat cancer. Your doctor will take these effects into account when deciding on your treatment.

Using Etoposide with food and drink
Etoposide is not affected by food or drink.

Pregnancy and breastfeeding
You should not use Etoposide if you are pregnant. If you are pregnant you should inform your doctor immediately.
- Women of child bearing age should take effective contraceptive measures.

You should not breast feed during treatment with Etoposide.

Feathering children whilst taking Etoposide
It is advised for men to consider sperm collection (for cryo-conservation) before treatment with etoposide, because infertility after treatment can occur.
Driving and using machines
This medication can cause nausea and vomiting. Caution is advised in undertaking actions which require extra alertness, such as the use of machines and driving.

Important information about some of the ingredients of Etoposide
This medicinal product contains approximately 30% ethanol (alcohol), i.e. up to 1.5 g per dose. This is equivalent to 30 ml of beer or 12.5 ml of wine per dose. This may be dangerous for patients suffering from alcoholism and for patients in high-risk groups such as those with liver problems or epilepsy (fits). The amount of alcohol in this product may alter the effects of other medicines.

Etoposide contains 30 mg/ml of benzyl alcohol and must not be given to premature babies or new born babies. It may cause toxic and allergic reactions in infants and children up to 3 years old.

3. **HOW ETOPOSIDE IS GIVEN TO YOU**

Etoposide concentrate for solution for infusion will always be given to you by a healthcare professional. This medicine will be diluted with 0.9% sodium chloride or 5% dextrose and will be given to you as an infusion (a "drip") into a vein.

**How much of the injection will you receive and how often?**
- The dose of Etoposide will be individually determined by your doctor. The dose you are given depends on your size, it varies with your surface area. Technically, this is measured in square metres, and is worked out from your height and weight.
- You will receive one dose a day during 3 - 5 days, followed by a 10 - 20 days rest.
- The administration will take at least 30 minutes.
- Usually three or four treatments are given, but the duration of the treatment and the number of treatments is determined by the doctor and may vary for each patient.
- Etoposide may be given alone or in combination with other medicines.
- Your condition will be closely monitored during treatment. This routinely involves blood tests and controls of your liver function.

If you have any questions about your treatment schedule ask your doctor, pharmacist or nurse.

**If you are given too much Etoposide**
If you think you have received too much medicine consult your doctor or a nurse.

**If you missed a dose of Etoposide**
If you have missed a dose of your treatment, consult your doctor or a nurse.

4. **POSSIBLE SIDE EFFECTS**

Like all medicines, Etoposide can cause side effects, although not everybody gets them. You should discuss them with your doctor who will explain the risks and benefits of your treatment.

Some of the side effects can be lessened or treated by other medicines or therapy.

Tell your doctor immediately if you notice any of the following:
- unexplained bruising, reddish or purplish patches on the skin, nosebleeds and bleeding (these may be signs of a decrease in the number of blood platelets, those cells in the blood that help the blood to clot)
- infections
- severe allergic reactions such as fever, reddening of the face and neck, often with a sudden, subjective feeling of heat (flushing), rapid heartbeat, abnormal contraction of your lungs which can cause a cough and wheezing, abnormally low blood pressure and stopping of breathing

It may be necessary to stop your treatment with Etoposide.

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The following information is intended for medical or healthcare professionals only:

**Cytotoxicity**

Instructions on how to dilute, administer, store and dispose of Etoposide

**Dilution**

Etoposide 20 mg/ml concentrate for solution for infusion must be diluted immediately prior to use with either 5% dextrose in water, or 0.9% sodium chloride solution to give a final concentration of 0.2 to 0.4 mg/ml. At higher concentrations precipitation of etoposide may occur.

**Administration**

The usual dose of etoposide, in combination with other approved chemotherapeutic agents, ranges from 100-120 mg/m²/day via continuous infusion over 90 minutes for 3-5 days, followed by a resting period of 10-20 days.

Generally 3 to 4 chemotherapy cycles are administered. Dose and number of cycles should be adjusted to the level of bone marrow suppression and the reaction of the tumour.

In patients with renal function impairment the dose should be adjusted. Etoposide is intended for intravenous administration only.
Although not all of these side effects may occur, tell your doctor if they do occur, as they may need medical attention.

The following headings are used to organise the side effects in order of frequency:
- **Very common:** (may affect more than 1 in 10 users)
- **Common:** (may affect 1 to 10 users in 100)
- **Uncommon:** (may affect 1 to 10 users in 1,000)
- **Rare:** (may affect 1 to 10 users in 10,000)
- **Very rare:** (may affect 1 user in 10,000)

The side effects could include:

**Very Common side effects**
- you may produce less red blood cells (anemia) and platelets than normal. This will be monitored by your doctor during your treatment with regular blood tests.
- infection
- nausea
- vomiting
- loss of appetite
- reversible loss of hair (alopecia), sometimes progressing to total baldness
- feeling of tiredness due to anemia

**Common side effects**
- leukemia (causes of the blood) in addition to the cancers that you are being treated for
- bleeding
- allergic (hypersensitive) reactions such as fever, redness of the face and neck, often with a sudden, subjective feeling of heat (flushing), rapid heart beat, abnormal contraction of your lungs which can cause a cough and wheezing, abnormally low blood pressure and stopping of breathing
- redness of the skin
- facial and tongue swelling
- coughing
- sweating
- bluish discoloration of the skin and mucous membranes
- convulsions (fits)
- spasmodic closure of the voice box (larynx)
- abnormally high blood pressure
- fatigue and drowsiness
- low blood pressure causing dizziness when Etoposide is administered too quickly
- abdominal pain
- diarrhoea
- inflammation of the mucous membrane of the mouth
- problems with your liver including increase in liver blood test values (bilirubin, SGOT and alkaline phosphatase); your doctor will monitor your liver function with blood tests during your treatment

**Uncommon side effects**
- damage to nerves of the hand and feet
- irregular heartbeat
- heart attack
- abnormal contractions in your lungs, which can cause a cough and wheezing
- coughing
- spasmodic closure of your throat which makes it difficult to breathe in.
- inflammation of the mucous membranes
- inflammation of the gullet (oesophagus)
- rash
- hives
- darkening of skin (increase in pigmentation)
- itching

**Rare side effects**
- allergic (hypersensitive) reactions caused by benzyl alcohol
- stroke, occasionally in association with allergic reactions
- a feeling of weakness
- sensations such as burning, pricking, itching, or tingling
- reversible loss of vision
- temporary blindness
- inflammation of an optic nerve
- unusually high concentration of uric acid in the blood
- inflammation of a vein
UKPAR Etoposide 20 mg/ml concentrate for solution for infusion

- when you are receiving the infusion, if it leaks into the surrounding tissues then irritation and swelling may occur around the location of the leakage
- stopping breathing
- inflammation of the tissues in the lungs
- formation of scar tissue in the lungs
- constipation
- difficulty in swallowing
- taste impairment
- Etoposide can accumulate in your liver and kidneys, especially if you have liver or kidney problems

Very rare side effects
- a potentially life-threatening skin disorder accompanied by severe skin blisters and often scabs in the membranes of the mouth, nose, eyes, and the anal and genital areas.
- inflammatory, itching skin reddening following radiation therapy and subsequent treatment with a rash at the site of previous radiotherapy
- redness and pain of palms of hands and soles of feet

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE ETOPOSIDE

Keep out of the reach and sight of children.

Do not use Etoposide after the expiry date which is stated on the vial and carton after EXP. The expiry date refers to the last day of that month.

Keep the vial in the outer carton, in order to protect from light. Do not refrigerate or freeze.

After dilution the solution should be used immediately. If this is not possible, the diluted solution may be stored at 15 – 25 °C for not more than 12 hours.

Left-over of used solutions should be discarded. Solutions showing any signs of precipitation should not be used.

Avoid unnecessary contact with the fluid. Rinse skin immediately after contact with the solution. Be sure your doctor or nurse removes any syringes or vials for disposal.

6. FURTHER INFORMATION

What Etoposide contains:
- The active substance Etoposide. Each vial (5 ml) contains 100 mg Etoposide
- The other ingredients are benzyl alcohol, citric acid, ethanol, polysorbate 80 and macrogol 300.

What Etoposide looks like and contents of the pack

Etoposide Concentrate for solution for infusion is a clear to pale yellow solution packaged in clear glass vials containing 5 ml of solution. The vials are packed in carton boxes containing 1 or 10 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
APSLA Limited, Bayview House, 49 North Strand Road, Dublin 3, Ireland.

Manufacturers:
APC Pharmaceuticals & Chemicals (Europe) Ltd.
9th Floor, CP House, 97-107 Usbridge Road, Ealing, London W5 5TL

Distributed By:
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9th Floor, CP House, 97-107 Usbridge Road, Ealing, London W5 5TL

This leaflet was last approved in MM/YYYY.

To prevent the occurrence of hypotension, the infusion should be given over at least 30 minutes.

Storage of the prepared solution

Chemical and physical in-use stability has been demonstrated for 24 hours 15-25 °C.

From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally be not longer than 12 hours at 15 – 25 °C, unless dilution has taken place in a controlled and validated aseptic conditions.

Handling and disposal

The normal procedures for proper handling and disposal of anti-tumour medicinal products should be adopted:

- Staff should be trained to reconstitute the medicinal product.
- Pregnant staff should be excluded from working with this medicinal product.
- Staff handling this medicinal product during reconstitution should wear protective clothing including mask, goggles and gloves.
- All items for administration or cleansing, including gloves, should be placed in high-risk, waste disposal bags for high-temperature incineration.
- Liquid waste may be flushed with large amounts of water.
- Accidental contact with the skin or eyes should be treated immediately with copious amounts of water.
UKPAR Etoposide 20 mg/ml concentrate for solution for infusion

PL 33410/0052 & 0083

LABELLING

PL 33410/0052 – labelling is identical for PL 33410/0083 apart from PL number

Carton – single vial pack

Keep out of the reach and sight of children.

For intravenous use only

DILUTE BEFORE USE

Use as directed by a doctor.

Read the package leaflet before use.

If diluted in 0.9% sodium chloride or 5% dextrose, the solution should be used immediately.

If not used immediately, store no longer than 12 hours at 15-25°C.

Do not refrigerate or freeze.

Keep vial in the outer carton, in order to protect from light.

PL Holder:
APNLA Limited,
Bayview House,
49 North Strand Road,
Dublin 3, Ireland

Distributed By:
APC Pharmaceuticals & Chemicals (Europe) Limited,
9th Floor, CP House,
97-107 Uxbridge Road,
Ealing, London W5 5TL

PL 33410/0052

Etoposide 20 mg/ml Concentrate for solution for infusion

Excipients:
Macrogol 300, Polysorbate 80,
Benzy alcohol, Ethanol,
Citric acid (anhydrous)

Contains benzy alcohol and
must not be given to new born babies. May cause toxic reactions and allergic reactions in infants and children up to 3 years old.

Vial label

Pharmacode Area

OVER PRINTING AREA
UKPAR Etoposide 20 mg/ml concentrate for solution for infusion

PL 33410/0052 & 0083

Carton – 10 vial pack