SUMMARY OF PRODUCT CHARACTERISTICS
ETOPOSIDE "SEDOL" 20 mg/ml Concentrate for Solution for Infusion

1. NAME OF THE MEDICINAL PRODUCT

Etoposide "SEDOL" 20 mg/ml Concentrate for Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of concentrate for solution for infusion contains 20 mg etoposide.

Pack sizes:

2.5 ml vial = 50 mg etoposide | 5 ml vial = 100 mg etoposide | 10 ml vial = 200 mg etoposide | 20 ml vial = 400 mg etoposide | 50 ml vial = 1,000 mg etoposide

Excipients with known effect:

Benzyl alcohol 20 mg/ml. Ethanol 96% (v/v) 260.60 mg/ml. Polysorbate 80. For warnings, see section 4.4.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, light yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Etoposide is an antineoplastic agent for intravenous use. It can be used alone or in combination with other antineoplastic agents in the following conditions:

- Small-cell lung cancer.
- Resistant non-seminomatous testicular carcinoma.
- Acute myelomonocytic and myelocytic leukaemia (AML, FAB subtype M4 or M5) as part of combination therapy after failure of induction chemotherapy.

4.2 Posology and method of administration

General

Etoposide should be administered only by or under the direct supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Pregnant personnel should not handle chemotherapeutic agents.

Method of administration — IMPORTANT

ETOPOSIDE "SEDOL" MUST NOT BE GIVEN BY RAPID INTRAVENOUS INJECTION.

The concentrate for solution for infusion must be diluted before use (see section 6.6). Immediately before administration, the required dose must be diluted in glucose 5% or 0.9% sodium chloride solution for injection to a concentration of 0.2–0.4 mg/ml (usually not more than 0.25 mg/ml). It should then be administered by slow intravenous infusion over a period of not less than 30 minutes (usually 30–60 minutes). Longer infusion times may be required based on patient tolerance.

Hypotension following rapid IV administration has been reported; the infusion should always be given over at least 30–60 minutes.

Care should be taken to avoid extravasation. The infusion site should be closely monitored. In the event of skin or mucosa contact, wash immediately and thoroughly with soap and water. Use of gloves is recommended.

Posology — Adults

The recommended dose is 60–120 mg/m² IV per day for 5 consecutive days. The most frequently used schedules are 100 mg/m² for 5 days or 120 mg/m² on alternate days (days 1, 3 and 5). The course of treatment must not be repeated more often than at intervals of 10–20 days (haematological indications) or 21 days (non-haematological indications).

Repeated courses must not be given before the blood picture has been checked for signs of myelosuppression and found satisfactory. Patients should not begin a new cycle if the neutrophil count is <1,500 cells/mm³ or the platelet count is <100,000 cells/mm³, unless caused by malignant disease.

Dose adjustments

Dosage should be modified to account for the myelosuppressive effects of other drugs in the combination or the effects of prior radiotherapy or chemotherapy that may have compromised bone marrow reserve.

Subsequent doses should be adjusted if:

- Neutrophil count <500 cells/mm³ for more than 5 days or associated with fever or infection.
- Platelet count <25,000 cells/mm³.
- Any other Grade 3 or 4 toxicity develops.
- Renal clearance is <50 ml/min.

Renal impairment

Creatinine clearance (ml/min)	Recommended daily dose (% of standard dose)
>50	100%
15–50	75%
<15 (see section 4.3)	Contraindicated

Subsequent dosing should be based on patient tolerance and clinical effect.

Hepatic impairment

Etoposide should be used with caution in patients with hepatic dysfunction; see section 4.4.

Elderly

Dose adjustment is not necessary.

Paediatric population

Safety and efficacy in children have not been established.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe hepatic dysfunction.
- Severe renal impairment (creatinine clearance <15 ml/min).
- Severe myelosuppression.
- Intra-arterial or intra-cavitary injection.
- Breast-feeding (see section 4.6).
- Concomitant use of yellow fever vaccine or other live vaccines in immunosuppressed patients (see section 4.5).

4.4 Special warnings and precautions for use

Myelosuppression

Severe myelosuppression with resulting infection or bleeding may occur. Fatal myelosuppression has been reported following etoposide administration. Patients must be observed carefully and frequently both during and after therapy. The following studies should be obtained at the start of therapy and prior to each subsequent dose: platelet count, haemoglobin, white blood cell count and differential. Etoposide should not be administered to patients with neutrophil counts <1,500 cells/mm³ or platelet counts <100,000 cells/mm³, unless caused by malignant disease.

If prior radiotherapy or chemotherapy has been given, an adequate interval should be allowed to enable bone marrow recovery.

Hepatic and renal monitoring

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

Anaphylactic reactions

Physicians should be aware of the possible occurrence of anaphylactic reactions manifested by chills, fever, flushing, tachycardia, bronchospasm, dyspnoea and hypotension, which can be fatal. The infusion should be

terminated immediately; pressor agents, corticosteroids, antihistamines or volume expanders should be administered as appropriate. Anaphylactic reactions can occur with the initial dose.

Secondary leukaemia

The occurrence of acute leukaemia, which can occur with or without a preleukaemic phase, has been reported rarely in patients treated with etoposide in association with other antineoplastic drugs. A total cumulative dose of etoposide >2,000 mg/m² increases the risk of secondary acute non-lymphoblastic leukaemia. An 11q23 chromosomal abnormality has been observed in some cases; the latency period averages approximately 32 months.

Mutagenic and carcinogenic potential

Etoposide is mutagenic and potentially carcinogenic. This should be taken into consideration when designing long-term therapy. An effective contraception is required for both male and female patients during treatment and for up to 6 months after treatment. Genetic consultation is recommended if the patient wishes to have children after ending treatment. As etoposide may decrease male fertility, preservation of sperm may be considered.

Bacterial infections

Bacterial infections must be brought under control before initiation of treatment with etoposide.

Excipients with known effect

Benzyl alcohol (20 mg/ml):

This product contains 20 mg benzyl alcohol per ml. Etoposide "SEDOL" should not be administered to premature infants or neonates, or to children younger than 6 months, due to the risk of metabolic acidosis.

Ethanol 96% (260.60 mg/ml):

At a dose of 120 mg/m² etoposide in a patient with a body surface area of 1.6 m², the patient would receive approximately 2.5 g ethanol. This must be taken into account when administering to patients with a history of alcohol abuse or patients receiving disulfiram.

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. Exercise caution in premature infants.

Plastic devices made of acrylic or ABS polymers have been reported to crack when used with undiluted etoposide concentrate; this effect has not been reported after dilution as instructed (see section 6.6).

4.5 Interaction with other medicinal products and other forms of interaction

Ciclosporin:

High-dose ciclosporin (concentrations >2,000 ng/ml) administered with oral etoposide has led to an 80% increase in etoposide exposure (AUC) and a 38% decrease in total body clearance. Etoposide may potentiate the cytotoxic and myelosuppressive effect of other drugs including ciclosporin.

Cisplatin:

Concomitant cisplatin therapy is associated with reduced total body clearance of etoposide.

Phenytoin:

Concomitant phenytoin therapy is associated with increased etoposide clearance and reduced efficacy.

Myelosuppressive agents:

Prior or concurrent use of other drugs with similar myelosuppressant action may have additive or synergistic effects.

Oral anticoagulants (warfarin):

The effect of oral anticoagulants may be increased. Concomitant warfarin therapy may result in elevated INR. Close monitoring of INR is recommended.

Protein binding:

In vitro plasma protein binding of etoposide is 97%. Phenylbutazone, sodium salicylate and salicylic acid may affect the protein binding of etoposide.

Live vaccines (contraindicated):

Vaccination of immunocompromised patients with live attenuated vaccines may result in severe and fatal infections. Yellow fever vaccine is contraindicated; other live vaccines should also be avoided.

Potentially beneficial interactions:

Etoposide has been found to have therapeutic synergy with a range of cytotoxic drugs including methotrexate and cisplatin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Etoposide is suspected to cause serious birth defects when administered during pregnancy. It has been shown to be teratogenic in mice and rats. There are no adequate and well-controlled studies in pregnant women. Etoposide should not be used during pregnancy unless clearly necessary. Women of childbearing potential must use effective contraception during treatment. If etoposide is used during pregnancy, or if pregnancy occurs during treatment, appropriate prenatal counselling should be provided and the benefit of treatment weighed against the possible risk to the foetus.

Breast-feeding

It is not known if etoposide is secreted in human breast milk; a risk to the suckling child cannot be excluded. Etoposide is strictly contraindicated during lactation; breast-feeding should be interrupted during treatment.

Fertility

Effective contraception is required for both male and female patients during treatment and up to 6 months after ending treatment. Etoposide may decrease male fertility; preservation of sperm may be considered. Genetic consultation is recommended for patients wishing to have children after treatment. In women, amenorrhoea, anovulatory cycles, decreased fertility and hypomenorrhoea have been reported.

4.7 Effects on ability to drive and use machines

No specific studies on the effect on the ability to drive and use machines have been performed. If the patient experiences fatigue or somnolence, driving or operating machinery should be avoided.

4.8 Undesirable effects

Summary of the safety profile

Dose-limiting bone marrow suppression (myelosuppression) is the most significant toxicity associated with etoposide. Nausea and vomiting are the major gastrointestinal toxicities. Reversible alopecia occurs in up to 66% of patients treated with etoposide.

System Organ Class	Very common	Common	Uncommon/Rare
Blood/lymphatic system	Myelosuppression*, leukopenia, thrombocytopenia, neutropenia, anaemia	Infections and haemorrhage following severe myelosuppression	Fever, sepsis
Neoplasms		Acute leukaemia (with or without preleukaemic phase)	
Immune system		Anaphylactic reactions**	Hypersensitivity reactions
Metabolism			Hyperuricaemia, tumour lysis syndrome
Nervous system		Peripheral neuropathy, CNS effects (1–3%), dizziness	Convulsion, optic neuritis, somnolence, fatigue, confusion, seizures***
Cardiac			Myocardial infarction, arrhythmias
Vascular		Transient hypotension after rapid IV administration, hypertension, phlebitis	
Respiratory			Apnoea, fatal bronchospasm, cough, laryngospasm, cyanosis, interstitial pneumonitis/pulmonary fibrosis, pneumonia
Gastrointestinal	Abdominal pain, nausea/vomiting (30–40%), diarrhoea (1–13%), anorexia (10–13%)	Mucositis (stomatitis, oesophagitis)	Dysphagia, dysgeusia

System Organ Class	Very common	Common	Uncommon/Rare
Hepatobiliary	Hepatotoxicity		Increase in liver enzymes
Skin	Reversible alopecia (up to 66%), pigmentation		Facial/tongue oedema, sweating, rash, urticaria, pruritus; rarely SJS, TEN, radiation recall dermatitis
Renal/urinary			Accumulation with renal impairment
Reproductive			Amenorrhoea, anovulatory cycles, decreased fertility, hypomenorrhoea
General	Asthenia, malaise	Extravasation****	

** Myelosuppression with fatal outcome has been reported. ** Anaphylactic reactions can be fatal. A higher frequency has been reported in children at infusion concentrations higher than recommended. *** Seizure is occasionally associated with allergic reactions. **** Post-marketing extravasation complications include local soft tissue toxicity, swelling, pain, cellulitis and necrosis.*

Haematological toxicity

Myelosuppression is most often dose-limiting. Bone marrow recovery is usually complete by day 20; no cumulative toxicity has been reported. Granulocyte and platelet nadirs tend to occur 10–14 days after administration. Leukopenia occurred in 60–91% and severe leukopenia (< 1,000 cells/mm³) in 7–17% of patients. Thrombocytopenia occurred in 28–41% and severe thrombocytopenia (< 50,000 platelets/mm³) in 4–20% of patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the National Regulatory Authority.

4.9 Overdose

Total doses of 2.4–3.5 g/m² administered IV over 3 days have resulted in severe mucosal inflammation and myelotoxicity. Metabolic acidosis and severe hepatic toxicity have been reported at doses higher than recommended. No specific antidote is available; symptomatic and supportive treatment must be given and patients closely monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, podophyllotoxin derivatives. ATC code: L01CB01.

Etoposide is a semisynthetic derivative of podophyllotoxin with significant cytotoxic activity. Etoposide affects the function of topoisomerase II (DNA-opening enzyme) and inhibits DNA synthesis in the terminal phase, resulting in cleavage of single and double stranded DNA. Cell death occurs in relation to the concentration and duration of exposure. Etoposide is phase-specific with cell stop in S and early G2-phases of the cell cycle; unlike other podophyllum compounds, it does not cause accumulation in the metaphase but prevents the cell from mitosis or destroys cells preparing for mitosis.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of etoposide show substantial interindividual variation. It is rapidly distributed and approximately 94% bound to plasma proteins (phenylbutazone, sodium salicylate and salicylic acid may affect protein binding). Plasma decay kinetics follow a bi-exponential curve (two-compartment model): distribution half-life approximately 1.5 hours; terminal elimination half-life 4–11 hours. Total body clearance values range from 33–38 ml/min, independent of dose over the range 100–600 mg/m². AUC and Cmax increase linearly with dose. Average volume of distribution is approximately 32% of body weight. Etoposide shows relatively poor penetration into CSF. Approximately 45% of an administered dose is excreted in urine (approximately one third within 72 hours). Only 6% or less is recovered in the bile.

5.3 Preclinical safety data

Reproduction toxicity:

Etoposide is teratogenic in rats at doses lower than those used clinically on an applied dose basis.

Mutagenicity:

Positive results from in vitro and in vivo genetic toxicity and chromosomal aberration studies indicate that etoposide is mutagenic.

Carcinogenicity:

Animal trials to determine carcinogenicity have not been performed. Based on the DNA-damaging effect and mutagenic potential, etoposide should be considered potentially carcinogenic in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol (20 mg/ml; excipient with known effect), ethanol 96% (v/v) (260.60 mg/ml; excipient with known effect), anhydrous citric acid, Macrogol 300, Polysorbate 80 (excipient with known effect).

6.2 Incompatibilities

Etoposide should not be physically mixed with any other drug except for the medicinal products declared in section 6.6.

Plastic devices made of acrylic or ABS polymers have been reported to crack when used with undiluted concentrate; this effect has not been reported after dilution according to instructions.

6.3 Shelf life

Concentrate (before reconstitution): 3 years. Diluted solution: 24 hours at room temperature or up to 24 hours at 2–8°C.

6.4 Special precautions for storage

No special precautions for storage for the concentrate. Chemical and physical in-use stability of the diluted solution has been demonstrated for 24 hours at room temperature. From a microbiological point of view, the diluted product should be used immediately; if not used immediately, in-use storage times and conditions are the responsibility of the user and normally should not exceed 24 hours at 2–8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

Amber Type I glass vials (Ph.Eur.) closed with fluoropolymer-coated chlorobutyl rubber stoppers (Ph.Eur.), with or without a protective plastic overwrap (ONKO-SAFE). Pack sizes: 1, 5 or 10 vials.

Nominal vial capacities and contents: 5 ml (50 mg/2.5 ml and 100 mg/5 ml), 10 ml (200 mg/10 ml), 20 ml (400 mg/20 ml) and 50 ml (1,000 mg/50 ml). Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handle according to guidelines for cytotoxic substances.

The concentrate for solution for infusion must not be used undiluted. Before use, dilute with isotonic sodium chloride 0.9% or glucose 5% solution for infusion to a final concentration of 0.2–0.4 mg/ml (not exceeding 0.4 mg/ml due to risk of precipitation).

As with other potentially cytotoxic compounds, caution should be exercised when handling etoposide (gloves, protective clothing, mask). Contact with skin and mucous membranes should be avoided. If contact occurs, wash with water immediately. Only for intravenous use. Single use only. Unused solution should be discarded.

Syringes, containers, absorbent materials, solutions and any other contaminated material should be placed in a designated impervious container and incinerated in accordance with local procedures.

Only clear solutions practically free from particles should be used. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Cytotoxic agents should not be handled by pregnant personnel.

7. MARKETING AUTHORISATION HOLDER

VENUS REMEDIES LIMITED
India.

8. MARKETING AUTHORISATION NUMBER (PPB REGISTRATION NUMBER)

H2009/19891/468/R1

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

25 February 2026

10. DATE OF REVISION OF THE TEXT

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