Prescribing Information

Etoposide 20 mg/ml Concentrate for Solution for Infusion

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Presentation: Each 5ml, 10ml, 12.5ml, 20ml, 25ml, 50ml vial contains 100mg, 200mg, 250mg, 400mg, 500mg, 1000mg of Etoposide respectively.

Indications: *Testicular cancer*: in combination with other approved chemotherapeutic agents for the treatment of first line, recurrent or refractory testicular cancer in adults. *Small cell lung cancer*: in combination with other approved chemotherapeutic agents in adults. *Hodgkin's lymphoma*: in combination with other approved chemotherapeutic agents in adult and paediatric patients. *Non-Hodgkin's lymphoma*: in combination with other approved chemotherapeutic agents in adult and paediatric patients. *Acute myeloid leukaemia*: in combination with other approved chemotherapeutic agents in adult and paediatric patients. *Gestational trophoblastic neoplasia*: first line and second line therapy in combination with other approved chemotherapeutic agents for the treatment of high risk gestational trophoblastic neoplasia in adults. *Ovarian cancer*: in combination with other approved chemotherapeutic agents for the treatment of non-epithelial ovarian cancer in adults and for the treatment of platinum-resistant/refractory epithelial ovarian cancer in adults.

Dosage and Administration: Should only be administered and monitored under the supervision of a qualified physician experienced in the use of anti-neoplastic medicinal products. *Adult population:* Recommended dose is 50 to 100 mg/m^2/day on days 1 to 5 or 100 to 120 mg/m^2 on days 1, 3, and 5 every 3 to 4 weeks in combination with other drugs indicated in the disease to be treated. Dosage should be modified to take into account the myelosuppressive effects of other drugs in the combination or the effects of prior radiotherapy or chemotherapy which may have compromised bone marrow reserve. Doses after initial dose should be adjusted if neutrophil count is below 500 cells/mm^3 for more than 5 days. Also adjust dose in case of occurrence of fever, infections, or at a thrombocyte count below 25,000 cells/mm^3, which is not caused by the disease. Adjust follow up doses in case of occurrence of grade 3 or 4 toxicities or if renal creatinine clearance is below 50 ml/min. At decreased creatinine clearance of 15 to 50 mL/min a dose reduction by 25% is recommended. *Administration precautions*: Exercise caution in handling and preparation of etoposide. Skin reactions associated with accidental exposure may occur. Use of gloves is recommended. If contact with skin or mucosa, immediately wash the skin with soap and water and flush the mucosa with water. *Paediatric population*: This medicinal product contains Benzyl alcohol. Warnings and precautions to be considered prior to the start of treatment cycle. Hodgkin's lymphoma; non-Hodgkin's lymphoma; acute myeloid leukaemia: has been used in the range of 75 to 150 mg/m^2/day for 2 to 5 days in combination with other antineoplastic agents. Treatment regimen should be chosen according to the local standard of care. Ovarian cancer; small cell lung cancer; gestational trophoblastic neoplasia; testicular cancer: Safety and efficacy below 18 years of age have not been established. No recommendation on a posology can be made. *Elderly population* (age > 65 years old): No dosage adjustment, other than based on renal function. *Renal impairment*: Initial dose modification should be considered based on measured creatinine clearance as follows: > 50 mL/min = 100% of dose; 15-50 mL/min = 75% of dose. Patients with creatinine clearance less than 15 mL/min and on dialysis, further dose reduction is likely to be required as etoposide clearance is further reduced. Subsequent dosing in moderate and severe renal impairment should be based on patient tolerance and clinical effect. Since etoposide and its metabolites are not dialyzable, it can be administered pre- and post-haemodialysis. *Method of administration*: By slow intravenous infusion (usually over a 30 to 60 minute period). Refer to SmPC for instructions on dilution of the medicinal product before administration.

Contraindications: Hypersensitivity to the active substance or to any of the excipients; Lactation; Concomitant use of yellow fever vaccine or other live vaccines in immunosuppressed patients.

Warnings and Precautions: In all instances where the use of etoposide is considered for chemotherapy, the physician must evaluate need and usefulness of the drug against the risk

of adverse reactions. Most adverse reactions are reversible if detected early. If severe reactions occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. Reinstitution of therapy should be carried out with caution, and with consideration of the further need for the drug and close attention to possible recurrence of toxicity. *Myelosuppression*: Dose limiting bone marrow suppression is the most significant toxicity. Fatal myelosuppression has been reported following administration. Patients being treated must be observed for myelosuppression carefully and frequently both during and after therapy. The following haematological parameters should be measured at start of therapy and prior to each subsequent dose of etoposide: platelet count, haemoglobin, white blood cell count and differential. If radiotherapy or chemotherapy has been given prior to starting treatment, an adequate interval should be allowed to enable the bone marrow to recover. Should not be administered to patients with neutrophil counts less than 1,500 cells/mm^3 or platelet counts less than 100,000 cells/mm^3, unless caused by malignant disease. Doses subsequent to initial dose should be adjusted if neutrophil count less than 500 cells/mm^3 occurs for more than 5 days or is associated with fever or infection, if platelet count less than 25,000 cells/mm^3 occurs, if any grade 3 or 4 toxicity develops or if renal clearance is less than 50 ml/min. Severe myelosuppression with resulting infection or haemorrhage may occur. Bacterial infections should be brought under control before treatment. *Secondary leukaemia*: Occurrence of acute leukaemia, which can occur with or without myelodysplastic syndrome, has been described in patients treated with etoposide containing chemotherapeutic regimens. Neither the cumulative risk, nor the predisposing factors related to the development of secondary leukaemia are known. Roles of both administration schedules and cumulative doses of etoposide have been suggested, but have not been clearly defined. An 11q23 chromosome abnormality has been observed in some cases of secondary leukaemia in patients who have received epipodophyllotoxins. Abnormality has also been seen in patients developing secondary leukaemia after being treated with chemotherapy regimens not containing epipodophyllotoxins and in leukaemia occurring de novo. Another characteristic associated with secondary leukaemia in patients who have received epipodophyllotoxins appears to be a short latency period, with average median time to development of leukaemia being approximately 32 months. *Hypersensitivity*: Physicians should be aware of possible occurrence of an anaphylactic reaction, manifested by chills, pyrexia, tachycardia, bronchospasm, dyspnoea and hypotension, which can be fatal. Treatment is symptomatic. Etoposide should be terminated immediately, followed by the administration of pressor agents, corticosteroids, antihistamines, or volume expanders. In-line filters should not be used due to an increased risk for infusion-related hypersensitivity reactions. *Hypotension*: Should only be given by slow intravenous infusion (usually over a 30 to 60 minute period) since hypotension has been reported as a possible side effect of rapid intravenous injection. *Injection site reaction*: May occur during administration. Given the possibility of extravasation, recommended to closely monitor the infusion site for possible infiltration during drug administration. *Low serum albumin*: Associated with increased exposure to etoposide. Patients with low serum albumin may be at increased risk for etoposide-associated toxicities. *Impaired renal function*: In patients with moderate (CrCl =15 to 50 mL/min), or severe (CrCl <15ml/min) renal impairment undergoing haemodialysis, etoposide should be administered at a reduced dose. Haematological parameters should be measured and dose adjustments in subsequent cycles considered based on haematological toxicity and clinical effect in moderate and severe renal impaired patients. *Acute renal failure*: Mostly in children, reversible acute renal failure has been reported when high dose (2220 mg/m^2 or 60 mg/kg) etoposide and total body irradiation were used for haematopoietic stem cell transplantation. Renal function should be evaluated prior to and after etoposide administration until complete renal function recovery. *Impaired hepatic function*: These patients should regularly have their hepatic function monitored due to the risk of accumulation. *Tumour lysis syndrome*: Tumour lysis syndrome (sometimes fatal) has been reported following the use of etoposide in association with other chemotherapeutic drugs. Close monitoring is needed to detect early signs, especially in patients with risk factors such as bulky treatment-sensitive tumours, and renal insufficiency. Appropriate preventive measures should be considered in patients at risk. *Excipients*: Etoposide Injection contains 30.5% alcohol (ethanol), which corresponds to 240.64 mg of ethanol per ml of concentrate i.e up to 1.2 gm of ethanol per 5 ml vial, equivalent to 30 ml of beer or 12.55 ml of wine and up to 3 gm of ethanol per 12.5 ml vial, equivalent to 75 ml of beer or 31.4 ml of wine. There is a health risk to hepatic patients, alcoholics, epileptics, patients with organic brain diseases, pregnant women, breastfeeding women, and children, amongst others. The effect of other

drugs may be reduced or increased. Etoposide Injection also contains benzyl alcohol, which may cause allergic reactions. Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called “gasping syndrome”) in young children. Should not be given to newborn babies (up to 4 weeks old) or used for more than a week in young children (less than 3 years old). Caution should be exercised in pregnant or breast-feeding patients or if the patient has a liver or kidney disease, as large amounts of benzyl alcohol can build-up in the body and may cause side effects (“metabolic acidosis”). Etoposide Injection also contains polysorbate 80. In newborn infants a life-threatening syndrome of liver, cholestasis and renal failure, pulmonary deterioration, thrombocytopenia and ascites has been associated with an injectable vitamin E product containing polysorbate 80.

Fertility, Pregnancy & Lactation: *Women of childbearing potential/Contraception in males and females*: Women of childbearing potential should use appropriate contraceptive measures to avoid pregnancy during therapy. An effective contraceptive is required for both male and female patients during treatment and up to 6 months after ending treatment. Genetic consultation is recommended if the patient wishes to have children after ending treatment. *Pregnancy*: Etoposide can cause foetal harm when administered to pregnant women. Should not be used during pregnancy unless the clinical condition of the woman requires treatment with etoposide. If used during pregnancy, or if the patient becomes pregnant while receiving the drug, the patient should be informed of the potential hazard to the foetus. *Breast-feeding*: Etoposide is excreted in human milk. There is the potential for serious adverse reactions in nursing infants. A decision must be made whether to discontinue breast-feeding or to discontinue Etoposide, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. Benzyl alcohol is probably excreted into breast milk and can be orally absorbed by the infant. *Fertility*: Etoposide may decrease male fertility, preservation of sperm may be considered for the purpose of later fatherhood.

Adverse Events include:
Adverse events which could be considered serious: Infection (Including opportunistic infections like *pneumocystis jirovecii* pneumonia), acute leukaemia, myelosuppression, neutropenia, thrombocytopenia, anaphylactic reactions, angioedema, bronchospasm, tumour lysis syndrome, cortical blindness transient, optic neuritis, seizure, myocardial infarction, hypertension, haemorrhage, interstitial pneumonitis, pulmonary fibrosis, hepatotoxicity, Stevens- Johnsons syndrome, toxic epidermal necrolysis, acute renal failure.

Other Very Common adverse events: Anaemia, leucopenia, abdominal pain, anorexia, constipation, nausea and vomiting, alanine aminotransferase increased, alkaline phosphatase increased, aspartate amino transferase increased, bilirubin increased, alopecia, pigmentation, asthenia, malaise.

Other Common adverse events: Dizziness, arrythmia, transient systolic hypotension following rapid intravenous administration, diarrhoea, mucositis (including stomatitis and esophagitis), pruritus, rash, urticaria, extravasation, phlebitis.

See SmPC for details of other adverse events.

Presentation and Price: 100mg/5ml x 1 vial £16.25, 500mg/25ml x 1 vial £81.42.

Legal Category: POM

Further information is available from: Accord-UK Ltd, Whiddon Valley, Barnstaple, Devon, EX32 8NS.

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard
Adverse events should also be reported to Accord-UK LTD on 01271 385257 or email medinfo@accord-healthcare.com.