For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

FYTOSID
Etoposide
Injection 20 mg/ml

WARNINGS
Etoposide Injection should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Severe myelosuppression with resulting infection or bleeding may occur.

DESCRIPTION:
Etoposide is a semisynthetic derivative of podophyllotoxin used in the treatment of wide variety of neoplasms.

Etoposide is a white crystalline powder. It is sparingly soluble in methanol and chloroform, slightly soluble in ethanol and very slightly soluble in water or ethyl ether.

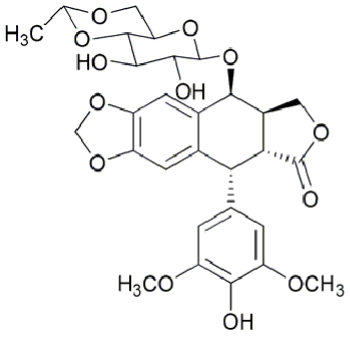
Etoposide injection is a clear, almost colourless to pale yellow solution.

COMPOSITION:

Each ml contains:

Etoposide USP	20.0 mg
Benzyl alcohol	2.8% v/v
Dehydrated alcohol	30.5% v/v

CHEMICAL STRUCTURE:



Chemical name is 4'-demethylepipodophyllotoxin 9-[4, 6-O-(R)-ethylidene-β-D-glucopyranoside]. Chemical formula is $C_{29}H_{32}O_{13}$. Molecular weight - 588.6.

PHARMACOLOGY:

Mechanism of action
Etoposide causes the induction of DNA strand breaks by an interaction with DNA-topoisomerase II or the formation of free radicals, leading to cell cycle arrest, primarily at the G2 stage of the cell cycle, and cell death.

INDICATIONS:
Small cell lung carcinoma, lymphosarcoma, acute monocytic and myelomonocytic leukemia, testicular tumor.

CONTRAINDICATIONS:
FYTOSID is contraindicated in the following patients:
- Patients with severe bone marrow depression
- Patients who have demonstrated severe hypersensitivity to this drug
- FYTOSID contains benzyl alcohol, it is contraindicated in neonates, prematures
- FYTOSID must not be given by intracavitary injection.

ADVERSE EFFECTS:
Hematological: leukopenia, thrombocytopenia, bleeding, anemia may occur.
Hepatic: hepatic function disorder such as elevations of GOT, GPT, ALP may occur.
Renal: elevations of BUN, creatinine may occur.
Gastrointestinal: nausea, vomiting, anorexia, stomatitis, diarrhea, abdominal pain, constipation may occur.
Hypersensitivity reactions: rash may occur.
Dermatologic: severe alopecia, erythema, pruritus may occur.
Nervous system: carpopedal numbness, headache may occur.
Respiratory: occasionally, ECG abnormality, arrythmia, hypotension may occur.
Others: malaise, flush may occur.
General precautions: severe adverse reactions including bone marrow depression (Myelosuppression) may occur, should therefore be observed the patient's condition and also frequent clinical test (hematologic, hepatic, renal, tests, etc) are performed. If any symptoms are founded, the drug should be reduced in dosage or discontinued, and appropriate corrective measures should be taken.
Since long-term therapy may occur serious adverse reaction or become chronic, the administration should be cautioned.
Manifestation or ingravescence of bleeding tendency should be cautioned.
Infection : Including opportunistic infections like pneumocystis jirovecii pneumonia.
Use in pediatric should be especially considered about manifestation of adverse reaction and the administration cautioned.
In use in children or patients of child bearing age, the influence on gonad should be considered.

Reporting of suspected adverse reactions
Reporting suspected adverse reaction after authorization of the medicinal product is important. It allows continued monitoring the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system :
Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan (BPOM RI)
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560, Indonesia

Email: pv-center@pom.go.id
Website: https://e-meso.pom.go.id
and/or through the following contact: pv.indonesia@fresenius-kabi.com

DRUG INTERACTIONS:
Cisplatin: Co-administration of cisplatin may increase exposure to etoposide.

Other antineoplastic agents or radiotherapy: adverse effects including bone marrow depression may vary by concomitant administration with other antineoplastic agents or radiotherapy.

PRECAUTIONS AND WARNINGS:

Etoposide Injections should be with caution administered in the following patients:

Myelosuppression
Etoposide causes myelosuppression that results in thrombocytopenia and neutropenia. Fatal infections and bleeding have occurred. Obtain complete blood counts prior to each cycle of Etoposide and more frequently as clinically indicated.

Hepatic Impairment
Etoposide should be with caution administered in patients with hepatic impairment.

Complication of Injection
Etoposide should be with caution administered in patients who have complication of injection.

Chicken Pox
Etoposide should be with caution administered in patients with chicken pox (fetal systemic symptom may appear).

Secondary Leukemias
Secondary leukemias have occurred with long term use of Etoposide.

Hypersensitivity Reactions
Etoposide can cause hypersensitivity reactions, including rash, urticaria, pruritus, and anaphylaxis. If hypersensitivity reactions occur, immediately interrupt Etoposide and institute supportive management. Permanently discontinue Etoposide in patients who experience a severe hypersensitivity reaction.
An increased risk for infusion-related hypersensitivity reactions was observed when inline filters were used during etoposide administration. In-line filters should not be used.

Etoposide should be administered by individuals experienced in the use of antineoplastic therapy. When Etoposide is administered intravenously care should be taken to avoid extravasation.

Radiotherapy / Chemotherapy
If radiotherapy and/or chemotherapy has been given in the use of antineoplastic therapy, interval should be allowed to enable the bone marrow to recover.

If the leucocyte count falls below 2,000/m^3, treatment should be suspended until the circulating the blood elements have returned to acceptable levels (platelets above 100,000/m^3 leucocytes above 4,000/mm^3) with recovery about 21 days after the last dose. Peripheral blood counts and liver function should be monitored.

Embryo-Fetal Toxicity
Based on animal studies and its mechanism of action, Etoposide can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential hazard to the fetus.

Advise females of reproductive potential to use effective contraception during treatment with Etoposide and for at least 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose.

Use in Pregnancy and Lactations
In animal studies, teratogenesis has been reported. Therefore, the drug should not be administered to the pregnant women or the suspected women of pregnancy. In animal studies, the drug has been excreted in milk. Use in nursing mother should be avoided nursing.

Etoposide Injection containing benzyl alcohol as preservative and administration of benzyl alcohol in premature infants has been associated with fatal gasping syndrome. Since benzyl alcohol can pass through the placenta, pregnant women should use etoposide and benzyl alcohol with caution. Excretion through breast milk is unclear, so it should be used with caution.

Females and Males of Reproductive Potential
Females
Advise females of reproductive potential to use effective contraception during treatment with Etoposide and for 6 months after the final dose.

Males
Etoposide may damage spermatozoa and testicular tissue, resulting in possible genetic fetal abnormalities. Males with female sexual partners of reproductive potential should use effective contraception during treatment with Etoposide and for 4 months after the final dose.

Infertility
Females
In females of reproductive potential, Etoposide may cause infertility and result in amenorrhea. Premature menopause can occur with Etoposide. Recovery of menses and ovulation is related to age at treatment.

Males
In male patients, Etoposide may result in oligospermia, azoospermia, and permanent loss of fertility.

Pediatric Use
Do not use for more than a week in young children (less than 3 years old), unless advised by your doctor or pharmacist.

Acute Leukemia
In the treatment of acute leukemia, peripheral vessel and bone marrow should be regularly monitored and also period of the administration should be reduced or prolonged.

Pharmaceutical Precautions
Etoposide should not be administered subcutaneously or intramuscularly.
IV administration may occur vascular pain, phlebitis, hypotension, arrythmia, therefore, injection site and administration method should be considered. And rate of injection should be as slow as possible.

When Etoposide is administered intravenously care should be taken to avoid extravasation. Etoposide should be diluted to the concentration of not more than 0.4 mg/ml to avoid precipitation. the reconstituted solution should be used immediately after reconstitution.

DOSAGE AND ADMINISTRATION:

The recommended course of Etoposide Injection is 60 - 100 mg/m^2, IV infusion, daily for five consecutive days. As Etoposide produces myelosuppression, courses may not be repeated more frequently than at 3 weeks intervals, but the dosage may vary according to symptom.

Immediately before administration, the require dose of Etoposide Injection must be diluted with either 5% Dextrose Injection USP or 0.9% Sodium Chloride Injection USP to give a solution concentration of 0.2 to 0.4 mg/mL of Etoposide; it should then be given by intravenous infusion over a period of 30 to 60 minutes.

Administration Precautions
Etoposide should be administered by individuals experienced in the use of antineoplastic therapy. When etoposide is administered intravenously, care should be taken to avoid extravasation. Skin reactions associated with accidental exposure to etoposide may occur. The use of gloves is recommended. If etoposide solution contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water.

Preparation for Intravenous Administration
Etoposide Injection must be diluted prior to use with either 5% Dextrose Injection USP or 0.9% Sodium Chloride Injection USP to give a final concentration of 0.2 to 0.4 mg/ml. If solutions are prepared at concentrations above 0.4 mg/ml, precipitation may occur.

Solutions showing any signs of precipitation should not be used. Hypotension following rapid intravenous administration has been reported; hence, it is recommended that the etoposide solution be administered over a 30-to-60-minute period. A longer duration of administration may be used if the volume of fluid to be infused is a concern. Etoposide should not be given by rapid intravenous injection.

STORAGE:
Preserve in hermetic containers. Store below 30°C. Protect from light.
For storage conditions after reconstitution of the medicinal product, see section “SHELF LIFE”.

INCOMPATIBILITIES:
Etoposide Injection should not be physically mixed with any other drug.

SHELF LIFE:
After dilution:
Chemical and physical in-use stability of the solution diluted with either 5% Dextrose Injection USP or 0.9% Sodium Chloride Injection USP to a concentration of 0.2 mg/ml or 0.4 mg/ml has been demonstrated up to 24 hours at 15°C to 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°C to 25°C, unless dilution has taken place in controlled and validated aseptic conditions.

HANDLING AND DISPOSAL:
Caution should be exercised when handling etoposide. Procedures for proper handling and disposal of anticancer drugs should be utilized. Several guidelines on this subject have been published.

To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing etoposide.

PRESENTATION:
FYTOSID (Etoposide Injection) is available as 5 ml injection containing 100 mg of etoposide.

List of excipients : Macrogol 300, Benzyl alcohol, Polysorbate 80, Dehydrated alcohol, Citric

Acid Monohydrate, Sodium Citrate

HARUS DENGAN RESEP DOKTER

MANUFACTURER INFORMATION:

Manufactured in India by:
Fresenius Kabi Oncology Ltd.
Village - Kishanpura,
P.O. Guru Majra, Tehsil - Nalagarh,
Distt. Solan, (H.P.) - 174 101

Imported by:
PT. FRESENIUS KABI COMBIPHAR
Bandung Barat - Indonesia

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DATE OF RELEASE: DD MMM YYYY