Product Name: Topoxin Injection	**Generic Name: Etoposide USP 100 mg**
MODULE I: ADMINISTRATIVE AND PRODUCT INFORMATION	

Summary of Product Characteristics

Product Name: Topoxin Injection	**Generic Name: Etoposide USP 100 mg**
MODULE I: ADMINISTRATIVE AND PRODUCT INFORMATION	

1. Name of the Drug Product

Topoxin Injection

2. Qualitative and Quantitative Composition

FORMULATION PER VIAL/ BATCH

Product Name: Topoxin Injection
(Each 5 ml contains Etoposide USP 100 mg)

Filled Volume per Vial: 5.5 ml
Batch Size: 7,272 Vials/ 40.00 L

Sl. No.	Name of Materials	Specification	Quantity per 5 ml	Quantity per Batch	Used as
	ACTIVE SUBSTANCE:				
01	Etoposide (Injectable Grade)	USP	* 100.000 mg	* 800.000 gm	Active Material
	EXCIPIENTS:				
02	Polyethylene Glycol 400	USPNF	3.250 gm	26.000 Kg	Solubilizing Agent
03	Polysorbate 80 (Sorbitan Mono-oleate)	BP	400.000 mg	3.200 Kg	Wetting Agent
04	Citric Acid Anhydrous	BP	12.000 mg	96.000 gm	Buffering Agent
05	Benzyl Alcohol	BP	150.000 mg	1.200 Kg	Antimicrobial Preservative
06	Dehydrated Alcohol	USP	q.s. to 5.0 ml	q.s. to 40.00 L	Vehicle

Note:* Based on 100% potency

Prepared By:	Checked By:	Approved By:
29.11.17	29.11.17	29.11.17
Sharmin Islam Executive, PD	Md. Azim Uddin Group Manager, PD	Sujit Kumar Kundu VP, Research & Development

3. Pharmaceutical Form

Injection

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4. Clinical particulars

4.1 Therapeutic indications

Testicular cancer

ETOPOSIDE is indicated in combination with other approved chemotherapeutic agents for the treatment of first line, recurrent or refractory testicular cancer in adults.

Small cell lung cancer

ETOPOSIDE is indicated in combination with other approved chemotherapeutic agents for the treatment of small-cell lung cancer in adults.

Hodgkin's lymphoma

ETOPOSIDE is indicated in combination with other approved chemotherapeutic agents for the treatment of Hodgkin's lymphoma in adult and paediatric patients.

Non-Hodgkin's lymphoma

ETOPOSIDE is indicated in combination with other approved chemotherapeutic agents for the treatment of non-Hodgkin's lymphoma in adult and paediatric patients.

Acute myeloid leukaemia

ETOPOSIDE is indicated in combination with other approved chemotherapeutic agents for the treatment of acute myeloid leukaemia in adult and paediatric patients.

Gestational trophoblastic neoplasia

ETOPOSIDE is indicated for 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

ETOPOSIDE is indicated in combination with other approved chemotherapeutic agents for the treatment of non-epithelial ovarian cancer in adults.

ETOPOSIDE is indicated for the treatment of platinum-resistant/refractory epithelial ovarian cancer in adults.

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4.2 Posology and method of administration

ETOPOSIDE should only be administered and monitored under the supervision of a qualified physician experienced in the use of anti-neoplastic medicinal products.

Adult population

The recommended dose of ETOPOSIDE in adult patients is 50 to 100 mg/m^2/day (etoposide equivalent) 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 (see section 4.4) which may have compromised bone marrow reserve. The doses after the initial dose should be adjusted if neutrophil count is below 500 cells/mm^3 for more than 5 days. In addition, the dose should be adjusted 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. Follow up doses should be adjusted 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: As with other potentially toxic compounds, caution should be exercised in handling and preparing the solution of ETOPOSIDE. 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 wash the skin with soap and water and flush the mucosa with water.

Elderly population

No dosage adjustment is necessary in elderly patients (age > 65 years old), other than based on renal function.

Paediatric population

Hodgkin's lymphoma; non-Hodgkin's lymphoma; acute myeloid leukaemia

ETOPOSIDE in paediatric patients has been used in the range of 75 to 150 mg/m^2/day (etoposide equivalent) for 2 to 5 days in combination with other antineoplastic agents. The treatment regimen should be chosen according to the local standard of care.

Ovarian cancer; small cell lung cancer; gestational trophoblastic neoplasia; testicular cancer

The safety and efficacy of ETOPOSIDE below 18 years of age have not been established.

Renal Impairment

In patients with impaired renal function, the following initial dose modification should be considered based on measured creatinine clearance.

Measured Creatinine Clearance	Dose of Etoposide Phosphate
>50 mL/min	100% of dose
15-50 mL/min	75% of dose

In 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 in these patients. 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

Infusion

Etoposide phosphate is administered by slow intravenous infusion (usually over a 30-to-60-minute period).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

ETOPOSIDE should only be administered and monitored under the supervision of a qualified physician experienced in the use of anti-neoplastic medicinal products. In all instances where the use of ETOPOSIDE is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risk of adverse reactions. Most such 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 according to the clinical judgment of the physician. Reinstitution of ETOPOSIDE therapy should be carried out with

caution, and with adequate 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 associated with ETOPOSIDE therapy. Fatal myelosuppression has been reported following etoposide phosphate administration. Patients being treated with ETOPOSIDE must be observed for myelosuppression carefully and frequently both during and after therapy. The following haematological parameters should be measured at the 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 etoposide treatment, an adequate interval should be allowed to enable the bone marrow to recover. ETOPOSIDE 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 with ETOPOSIDE.

Secondary leukaemia

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. Neither the cumulative risk, nor the predisposing factors related to the development of secondary leukaemia are known. The 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. This 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 that has been 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 the possible occurrence of an anaphylactic reaction with ETOPOSIDE, 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 at the discretion of the physician.

Hypotension

ETOPOSIDE should be given only 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

Injection site reactions may occur during administration of ETOPOSIDE. Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration.

Low serum albumin

Low serum albumin is associated with increased exposure to etoposide. Therefore, 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 <15 mL/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.

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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

Patients with impaired hepatic function 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 of patients is needed to detect early signs of tumour lysis syndrome, especially in patients with risk factors such as bulky treatment-sensitive tumours, and renal insufficiency. Appropriate preventive measures should also be considered in patients at risk of this complication of therapy.

Mutagenic potential

Given the mutagenic potential of etoposide, an effective contraception 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 the treatment. As etoposide may decrease male fertility, preservation of sperm may be considered for the purpose of later fatherhood.

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per 100 mg vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other drugs on the pharmacokinetics of etoposide phosphate

High dose ciclosporin, resulting in plasma concentrations above 2000 ng/mL, administered with oral etoposide has led to an 80% increase in etoposide exposure (AUC) with a 38% decrease in total body clearance of etoposide compared to etoposide alone.

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

Concomitant phenytoin therapy is associated with increased etoposide clearance and reduced efficacy, and other enzyme-inducing antiepileptic therapy may be associated with increased ETOPOSIDE clearance and reduced efficacy.

As etoposide phosphate is converted *in vivo* to etoposide by phosphorylation, caution should be exercised when administering etoposide phosphate with drugs that are known to inhibit phosphatase activity as such combination may reduce efficacy of etoposide phosphate.

In vitro plasma protein binding is 97%. Phenylbutazone, sodium salicylate and acetylsalicylic acid (aspirin) may displace etoposide from plasma protein binding.

Effect of etoposide phosphate on the pharmacokinetics of other drugs

Co-administration of antiepileptic drugs and ETOPOSIDE can lead to decreased seizure control due to pharmacokinetic interactions between the drugs.

Co-administration of warfarin and etoposide may result in elevated international normalized ratio (INR). Close monitoring of INR is recommended.

Pharmacodynamic interactions

There is increased risk of fatal systemic vaccinal disease with the use of yellow fever vaccine. Live vaccines are contraindicated in immunosuppressed patients.

Prior or concurrent use of other drugs with similar myelosuppressive action as etoposide may be expected to have additive or synergetic effects.

Cross resistance between anthracyclines and etoposide has been reported in preclinical experiments.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential should use appropriate contraceptive measures to avoid pregnancy during etoposide therapy. Etoposide has been shown to be teratogenic in mice and rats. Given the mutagenic potential of etoposide, 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

There are no or limited amount of data from the use of etoposide phosphate in pregnant women. Studies in animals have shown reproductive toxicity. In general etoposide can cause fetal harm when administered to pregnant women. ETOPOSIDE should not be used during pregnancy unless the clinical condition of the woman requires treatment with etoposide. Women of childbearing potential should be advised to avoid becoming pregnant. Women of childbearing potential have to use effective contraception during and up to 6 months after treatment. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be informed of the potential hazard to the foetus.

Breastfeeding

Etoposide is excreted in human milk. There is the potential for serious adverse reactions in nursing infants from ETOPOSIDE. A decision must be made whether to discontinue breast-feeding or to discontinue ETOPOSIDE, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

As etoposide may decrease male fertility, preservation of sperm may be considered for the purpose of later fatherhood.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Etoposide phosphate may cause adverse reactions that affect the ability to drive or use machines such as fatigue, somnolence, nausea, vomiting, cortical blindness, hypersensitivity reactions with hypotension. Patients who experience such adverse reactions should be advised to avoid driving or using machines.

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4.8 Undesirable effects

Summary of the safety profile

Dose-climiting bone marrow suppression is the most significant toxicity associated with ETOPOSIDE therapy. In clinical studies in which ETOPOSIDE was administered as a single agent at a total dose of ≥450 mg/m^2 the most frequent adverse reactions of any severity were leukopenia (91%), neutropenia (88%), anaemia (72%) thrombocytopenia (23%), asthenia (39%), nausea and/or vomiting (37%), alopecia (33%) and chills and/or fever (24%).

Tabulated summary of adverse reactions

The following adverse reactions were reported from ETOPOSIDE clinical studies and post-marketing experience. These adverse reactions are presented by system organ class and frequency, which is defined by the following categories: 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).

System Organ Class	Frequency	Adverse Reaction (MedDRA Terms)
Infections and infestations	common	infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	common	acute leukaemia
Blood and lymphatic system disorders	very common	anaemia , leukopenia, myelosuppression*, neutropenia, thrombocytopenia
Immune system disorders	common	anaphylactic reactions**
	not known	angioedema, bronchospasm
Metabolism and nutrition disorders	not known	tumour lysis syndrome
Nervous system disorders	common	dizziness
	uncommon	neuropathy peripheral
	rare	cortical blindness transient, neurotoxicities (*e.g.*, somnolence and fatigue), optic neuritis, seizure***
Cardiac disorders	common	arrythmia, myocardial infarction
Vascular disorders	common	hypertension, transient systolic

		hypotension following rapid intravenous administration
	uncommon	haemorrhage
Respiratory, thoracic and mediastinal disorders	rare	interstitial pneumonitis, pulmonary fibrosis
	not known	bronchospasm
Gastrointestinal disorders	very common	abdominal pain, anorexia, constipation, nausea and vomiting
	common	diarrhoea, mucositis (including stomatitis and esophagitis)
	rare	dysgeusia, dysphagia
Hepatobiliary disorders	very common	alanine aminotransferase increased, alkaline phosphatase increased, aspartate amino transferase increased, bilirubin increased, hepatotoxicity
Skin and subcutaneous tissue disorders	very common	alopecia, pigmentation
	common	pruritus, rash, urticaria
	rare	Radiation recall reaction (dermatologic), Stevens-Johnsons syndrome, toxic epidermal necrolysis
Renal and urinary disorders	not known	acute renal failure
Reproductive system and breast disorders	not known	infertility
General disorders and administration site conditions	very common	asthenia, malaise
	common	extravasation****, phlebitis
	rare	pyrexia
*Myelosuppression with fatal outcome has been reported **Anaphylactic reactions can be fatal ***Seizure is occasionally associated with allergic reactions. ****Post-marketing complications reported for extravasation included local soft tissue toxicity, swelling, pain, cellulitis, and necrosis including skin necrosis.		

Description of selected adverse reactions

In the paragraphs below the incidences of adverse events, given as the mean percent, are derived from studies that utilized single agent ETOPOSIDE therapy.

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Haematological Toxicity

Myelosuppression with fatal outcome has been reported following administration of etoposide phosphate. Myelosuppression is most often dose-limiting. Bone marrow recovery is usually complete by day 20, and no cumulative toxicity has been reported. Granulocyte and platelet nadirs tend to occur about 10 to14 days after administration of etoposide phosphate depending on the way of administration and treatment scheme. Nadirs tend to occur earlier with intravenous administration compared to oral administration. Leukopenia and severe leukopenia (less than 1,000 cells/mm^3) were observed in 91% and 17%, respectively, for etoposide phosphate.

Thrombocytopenia and severe thrombocytopenia (less than 50,000 platelets/mm^3) were seen in 23% and 9% respectively, for etoposide phosphate. Reports of fever and infection were also very common in patients with neutropenia treated with etoposide phosphate. Bleeding has been reported.

Gastrointestinal Toxicity

Nausea and vomiting are the major gastrointestinal toxicities of etoposide phosphate. The nausea and vomiting can usually be controlled by antiemetic therapy.

Alopecia

Reversible alopecia, sometimes progressing to total baldness, was observed in up to 44% of patients treated with etoposide phosphate.

Hypotension

Transient hypotension following rapid intravenous administration has been reported in patients treated with etoposide phosphate and has not been associated with cardiac toxicity or electrocardiographic changes. Hypotension usually responds to cessation of infusion of etoposide phosphate and/or other supportive therapy as appropriate.

When restarting the infusion, a slower administration rate should be used. No delayed hypotension has been noted.

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Hypertension

In clinical studies involving etoposide phosphate, episodes of hypertension have been reported. If clinically significant hypertension occurs in patients receiving etoposide phosphate, appropriate supportive therapy should be initiated.

Hypersensitivity

Anaphylactic reactions have been reported to occur during or immediately after intravenous administration of etoposide phosphate. The role that concentration or rate of infusion plays in the development of anaphylactic reactions is uncertain. Blood pressure usually normalizes within a few hours after cessation of the infusion.

Anaphylactic reactions can occur with the initial dose of etoposide phosphate.

Anaphylactic reactions, manifested by chills, tachycardia, bronchospasm, dyspnoea, diaphoresis, pyrexia, pruritus, hypertension or hypotension, syncope, nausea and vomiting have been reported to occur in 3% (7 of 245 patients treated with ETOPOSIDE in 7 clinical studies) of patients treated with ETOPOSIDE. Facial flushing was reported in 2% of patients and skin rashes in 3%. These reactions have usually responded promptly to the cessation of the infusion and administration of pressor agents, corticosteroids, antihistamines, or volume expanders as appropriate.

Acute fatal reactions associated with bronchospasm have also been reported with etoposide phosphate. Apnoea with spontaneous resumption of breathing following cessation of infusion have also been reported.

Metabolic Complications

Tumour lysis syndrome (sometimes fatal) has been reported following the use of etoposide phosphate in association with other chemotherapeutic drugs.

Acute renal failure

Reversible acute renal failure has been reported in post-marketing experience.

Paediatric population

The safety profile between paediatric patients and adults is expected to be similar.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Total doses of 2.4 g/m^2 to 3.5 g/m^2 administered intravenously over three days have resulted in severe mucositis and myelotoxicity. Metabolic acidosis and cases of serious hepatic toxicity have been reported in patients receiving higher than recommended intravenous doses of etoposide. Similar toxicities can be expected with oral formulation. A specific antidote is not available. Treatment should therefore be symptomatic and supportive, and patients should be closely monitored. Etoposide and its metabolites are not dialyzable.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, antineoplastic agents, plant alkaloids and other natural products, podophyllotoxin derivatives,

ATC code: L01CB01

Mechanism of action

Etoposide phosphate is metabolised *in vivo* into the active substance etoposide by a process of dephosphorylation. The mechanism of action of etoposide phosphate is considered to be the same as that of etoposide.

The main effect of etoposide appears to be at the late S and early G_2 portion of the cell cycle in mammalian cells. Two dose-dependent responses are seen: At high concentrations (10 mcg/mL or more), cells entering mitosis are lysed; at low concentrations (0.3 to 10 mcg/mL), cells are inhibited from entering prophase.

Microtubule assembly is not affected. The predominant macromolecular effect of etoposide seems to be the rupture of the double strand by an interaction with DNA- topoisomerase II or

by the formation of free radicals. Etoposide has been shown to cause metaphase arrest in chick fibroblasts.

5.2 Pharmacokinetic properties

Absorption

After either intravenous infusion or oral capsule administration, the C_{max} and AUC values exhibit marked intra- and inter-subject variability.

Distribution

The mean volumes of distribution at steady state range from 18 to 29 litres . Etoposide shows low penetration into the CSF. *In vitro*, etoposide is highly protein bound (97%) to human plasma proteins.

Etoposide binding ratio correlates directly with serum albumin in cancer patients and normal volunteers. Unbound fraction of etoposide correlates significantly with bilirubin in cancer patients.

Biotransformation

The hydroxyacid metabolite [4' dimethyl-epipodophyllic acid-9-(4,6 0-ethylidene-β- D-glucopyranoside)], formed by opening of the lactone ring, is found in the urine of adults and children. It is also present in human plasma, presumably as the trans isomer. Glucuronide and/or sulfate conjugates of etoposide are also excreted in human urine. In addition, O-demethylation of the dimethoxyphenol ring occurs through the CYP450 3A4 isoenzyme pathway to produce the corresponding catechol.

Elimination

On intravenous administration, the disposition of etoposide is best described as a biphasic process with a distribution half-life of about 1.5 hours and terminal elimination half-life ranging from 4 to 11 hours. Total body clearance values range from 33 to 48 mL/min or 16 to 36 mL/min/m^2 and, like the terminal elimination half- life, are independent of dose over a range 100 to 600 mg/m^2. After intravenous administration of ^{14}C etoposide (100 to 124 mg/m^2), mean recovery of radioactivity in the urine was 56% (45% of the dose was excreted as etoposide) and faecal recovery of radioactivity was 44% of the administered dose at 120 hours.

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Linearity/non-linearity

Total body clearance and the terminal elimination half-life are independent of dose over a range 100 to 600 mg/m^2. Over the same dose range, the areas under the plasma concentration vs. time curves (AUC) and the maximum plasma concentration (C_{max}) values increase linearly with dose.

Renal impairment

Patients with impaired renal function receiving etoposide have exhibited reduced total body clearance, increased AUC and higher steady state volume of distribution.

Hepatic impairment

In adult cancer patients with liver dysfunction, total body clearance of etoposide is not reduced.

Elderly population

Although minor differences in pharmacokinetic parameters between patients ≤65 years and >65 years of age have been observed, these are not considered clinically significant.

Paediatric population

In children, approximately 55% of the dose is excreted in the urine as etoposide in 24 hours. The mean renal clearance of etoposide is 7 to 10 mL/min/m^2 or about 35% of the total body clearance over a dose range of 80 to 600 mg/m^2. Etoposide, therefore, is cleared by both renal and non-renal processes, i.e. metabolism and biliary excretion. The effect of renal disease on plasma etoposide clearance is not known in children. In children, elevated SGPT levels are associated with reduced drug total body clearance. Prior use of cisplatin may also result in a decrease of etoposide total body clearance in children.

An inverse relationship between plasma albumin levels and etoposide renal clearance is found in children.

Gender

Although minor differences in pharmacokinetic parameters between genders have been observed, these are not considered clinically significant.

Drug interactions

In a study of the effects of other therapeutic agents on in vitro binding of ^{14}C etoposide to human serum proteins, only phenylbutazone, sodium salicylate and acetylsalicylic acid (aspirin) displaced protein-bound etoposide at concentrations generally achieved in vivo.

5.3 Preclinical safety data

Chronic toxicity

Anaemia, leukopenia, and thrombocytopenia were observed in rats and mice, while dogs had mild reversible deterioration of liver and kidney functions. The dose multiple (based on mg/m^2 doses) for these findings at the no-observed adverse-effect- level in the preclinical studies were ≥ approximately 0.05 times compared to the highest clinical dose. Historically, preclinical species have been more sensitive compared to humans towards cytotoxic agents. Testicular atrophy, spermatogenesis arrest, and growth retardation were reported in rats and mice.

Mutagenicity

Etoposide is mutagenic in mammalian cells.

Reproductive toxicity

In animal studies etoposide was associated with dose-related embryotoxicity and teratogenicity.

Carcinogenic potential

Given its mechanism of action, etoposide phosphate should be considered a possible carcinogen in humans.

6. Pharmaceutical particulars

6.1 List of excipients

Polyethylene Glycol 400

Polysorbate 80

Citric Acid Anhydrous

Benzyl Alcohol

Dehydrated Alcohol

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6.2 Incompatibilities

Not applicable

6.3 Shelf life

03 years.

6.4 Special precautions for storage

Store the vial in original carton not exceeding 25°C. Protect from light. Keep out of the reach of the children.

6.5 Nature and contents of container

Primary Packaging: Glass Vial

Secondary Packaging: Paper bord carton

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder

CORPORATE OFFICE
Beacon Business Center
9/B/2, Toyenbee Circular Road, Motijheel, Dhaka- 1223, Bangladesh

Tel: +880-2-5716371-76,

Fax: 880-2-57165379

E-mail: beacon@beaconpharma.com.bd

Website: www. beaconpharma.com.bd

FACTORY
Bhaluka, Mymensingh, Bangladesh

8. Marketing authorization Number:

M.A. No. 341-117-10

9. Date of first authorization/renewal of the authorization

25.05.2010/24.05.2025

10. Date of revision of the text

23.04.2022