Getwell Pharmaceuticals
474, Udyog Vihar, Phase-V,
Gurgaon - 122 016, Haryana, INDIA

Etoposide Capsules

Section I - IDENTITY

Common/Trade Name: Etoposide Capsules

Chemical Names: Trans-Etoposide

Synonyms: 4-Demethylepipodophyllotoxin beta-D-ethylideneglucoside, 4'-Demethylepipodophyllotoxin 9-(4,6-O-(R)-ethylidene-beta-D-glucopyranoside), 9-((4,6-O-Ethylidine-beta-D-glucopyranosyl)oxy)-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,4-dimethyloxyphenyl)furo(3',4":6,7)naptho-(2,3-D)-1,3-dioxol-6(5ah)-one

Manufacturer's Name: GETWELL PHARMACEUTICALS
Address: 474, UDYOG VIHAR, PHASE-V,
GURGAON - 122 016, HARYANA, INDIA

Telephone Number for Info.: +91 124 4014 403 / 04

Date Prepared: March 12, 2017

Section II - HAZARDOUS INGREDIENTS/COMPOSITION INFORMATION

Chemical Entity:	CAS No:	Molecular formula:
Etoposide	33419-42-0	$C_{29}H_{32}O_{13}$

Refer to full PI for list of inactive ingredients.

Section III - HEALTH HAZARD DATA

Emergency Overview

Appearance	solid : opaque pink ; liquid filled gelatin capsule
Signal Word	Danger
Hazard Statements	May cause heritable genetic damage. May cause cancer. May impair fertility. May cause harm to the unborn child. Danger of serious damage to health by prolonged exposure. Target Organs: bone marrow, gastrointestinal tract, peripheral nervous system, lymphatic system, cardiovascular system, female reproductive organs, male reproductive organs.
Precautionary Measures	When handling broken or crushed tablets or capsules, ensure worker exposure is below the recommended exposure limit. Avoid ingestion, inhalation, skin and eye contact. Wash hands after handling to minimize exposure. Pregnant or nursing women should avoid exposure.

Potential Health Effects

Eyes	Not available
Skin	May cause skin irritation
Ingestion	Not available
Inhalation	Not available
Target Organs	bone marrow, gastrointestinal tract, peripheral nervous system, lymphatic system, cardiovascular system, female reproductive organs, male reproductive organs
Signs and Symptoms	Acute: nausea, vomiting, diarrhoea, loss of appetite, abdominal pain, thirst, dry mouth, chest pain, rash, asthma, breathing difficulties, difficulty swallowing, headache, dizziness, confusion, fatigue. Chronic: hair loss, nail changes, mouth effects, bruising, skin effects, eye effects, impairment of vision, tingling, numbness, other central nervous effects, pain, coma, menstrual irregularities, increased urine volume.
Medical Conditions Aggravated Include:	disorders affecting target organs

Environmental Effects Refer to Section 12

Section IV - FIRST AID MEASURES

Eye contact: Rinse immediately with plenty of water for at least 15 minutes. Keep eye wide open while rinsing. Obtain medical attention.

Skin contact: Take off contaminated clothing and shoes immediately. Wash off immediately with plenty of water for at least 15 minutes. Obtain medical attention. Discard contaminated clothing or wash before re-use.

Inhalation: Move to fresh air. Oxygen or artificial respiration if needed. Obtain medical attention.

Ingestion: Do NOT induce vomiting. Consult a physician if necessary. Never give anything by mouth to an unconscious person.

Notes to Physician This material is a finished drug product for patient use. It is used in the treatment of cancer. This product may cause: nausea, vomiting, diarrhoea, loss of appetite, abdominal pain, thirst, dry mouth, chest pain, rash, asthma, breathing difficulties, difficulty swallowing, headache, dizziness, confusion, fatigue, hair loss, nail changes, mouth effects, bruising, skin effects, eye effects, impairment of vision, tingling, numbness, other central nervous effects, pain, coma, menstrual irregularities, increased urine volume, decreased white blood cell count, changes in red blood cell parameters, acute leukemia, changes in blood clotting parameters, lowered blood pressure, cardiac irregularities, heart attack, congestive heart failure, colitis, inflammation of gastrointestinal tract, anaphylaxis, liver toxicity, peripheral neuropathies, ovarian changes, sperm abnormalities, kidney disorders, changes in clinical chemistry parameters. Organs affected may include: bone marrow, gastrointestinal tract, peripheral nervous system, lymphatic system, cardiovascular system, female reproductive organs, male reproductive organs. Medical conditions aggravated include: disorders affecting target organs. This product has been reported to interact with the following medications: cytotoxic and cytostatic medicines, cyclosporine. Refer to Section 11. Possible risk of harm to the unborn child. Pregnant or nursing women should avoid exposure.

Medical Surveillance A pre-placement physical examination and history for employees with potential exposure to this compound is recommended. Baseline testing would include: a complete blood count with differential, a blood test for liver function. Based on opportunity for exposure and duration of exposure a periodic follow-up examination may be considered.
Employees who are pregnant, are breast-feeding, or who are concerned with other reproductive issues should be encouraged to consult with the occupational health physician monitoring worker's health.

Section V - FIRE AND EXPLOSION HAZARD DATA

Flammable Properties: Not available

Extinguishing Media:
Suitable extinguishing media: Dry chemical, Water spray, Foam
Unsuitable extinguishing media: Do NOT use water jet.

Protection of Firefighters:
Specific hazards: Mutagen Teratogen
Protective equipment: Use personal protective equipment. In the event of fire, wear self-contained breathing apparatus.
Hazardous Combustion Products: carbon oxides(COx), trace titanium, trace iron oxides.

Other information: Decontaminate protective clothing and equipment before reuse.

Section VI - ACCIDENTAL RELEASE INFORMATION

Personal precautions: Refer to protective measures listed in sections 7 and 8. Use personal protective equipment. Examples include tightly fitting safety goggles, disposable lab coat of low permeability with cuffs, double gloves and shoe covers. Depending on the nature of the spill (quantity and extent of spill) additional protective clothing and equipment such as a self-contained breathing apparatus may be needed.

Environmental precautions: Prevent release to drains and waterways. Prevent release to the environment.

Containment Methods: Wet down any dust to prevent generation of aerosols, if appropriate. Cover with suitable material.

Cleanup Methods: Contain and collect spillage and place in container for disposal according to local regulations (see Section 13). Clean spill area with a deactivating solution (if available) followed by detergent and water after spill pick-up. Handle waste materials, including gloves, protective clothing, contaminated spill cleanup material, etc., as appropriate for chemically and pharmacologically similar materials.

Section VII - HANDLING AND STORAGE

Handling Precautions: Highly potent material. Avoid formation of dust and aerosols. Avoid exposure – obtain special instructions before use. When handling broken or crushed tablets or capsules, ensure worker exposure is below the recommended exposure limit. Keep away from heat and sources of ignition. Prevent release to drains and waterways.

Storage Conditions: Keep refrigerated. (2 - 8 °C) Do not freeze.

Container Requirements: Store in the original primary packaging as provided.

Section VIII - CONTROL MEASURES AND PERSONAL PROTECTIVE EQUIPMENT

Exposure limit(s)	Company Guideline	ACGIH	OSHA	NIOSH
Etoposide	0.14 µg/m3	--	--	--
Glycerol	--	10 mg/m3 TW	15 mg/m3 TWA 5 mg/m3 TWA	--
Red Iron Oxide	--	5 mg/m3 TWA dust and fume, as Fe 1 mg/m3 TWA as Fe	10 mg/m3 TWA	2,500 mg/m3 IDLH dust and fume, as Fe 5 mg/m3 TWA dust and fume, as Fe 1 mg/m3 TWA as Fe
Titanium Dioxide	--	10 mg/m3 TWA	15 mg/m3 TWA total	5,000 mg/m3 IDLH
Exposure Control Band	Etoposide ***5*** -- Material is assigned to Exposure Control Band 5 (range 0.1 – 1 µg/m3).			
Bristol-Myers Squibb Exposure Guidelines Summary	Etoposide Materials require particular care and handling. Adherence to this guideline should protect employees from experiencing the therapeutic and/or adverse effects of this drug.			
Recommended Industrial Hygiene Monitoring Methods	Contact the Bristol-Myers Squibb AIHA accredited Industrial Hygiene Laboratory at 732-227-7368. See Section 4 "Notes to Physician" for information on medical surveillance.			
Engineering Controls and Ventilation	When handling small quantities in a clinical setting, good room ventilation is desirable. Specific engineering controls should not be needed. When handling broken or crushed tablets or capsules, ensure worker exposure is below the recommended exposure limit. If significant dust is generated, use process			

	enclosures, containment technology, or other engineering controls to keep airborne levels below recommended exposure limit.
Respiratory protection	Normally not required for handling a small number of tablets/capsules. Use the indicated respiratory protection if the occupational exposure limit is exceeded and/or in case of product release (dust). Use and selection of respiratory protection is based upon engineering controls in use and potential for aerosol generation. When engineering controls are not sufficient to control exposure, wear an approved respirator with NIOSH Class 100 or high efficiency particulate (HEPA) filters or cartridges when exposures are up to 10 times the exposure control guideline. Wear a loose-fitting (Tyvek or helmet type) HEPA powered-air purifying respirator (PAPR) when exposures are 10-25 times the exposure control guideline. Wear a full facepiece negative pressure respirator with Class 100 or HEPA filters when exposures are 25-50 times the exposure control guideline. Wear a tight-fitting, full facepiece HEPA PAPR when exposures are 50-100 times the exposure control guideline. Wear a hoodshroud HEPA PAPR or full facepiece supplied air respirator operated in a pressure demand or other positive pressure mode when exposures are 100- 1000 times the exposure control guideline.
Eye protection	Safety glasses with side-shields are recommended.
Hand protection	Wear gloves at all times when handling containers, including when unpacking, inspecting or transporting within a facility. Disposable chemotherapy gloves made from nitrile, neoprene, polyurethane and natural latex have been shown to have low permeability to many chemotherapy agents. Persons who are allergic to natural rubber latex should select gloves made from one of the other materials. Check gloves frequently to ensure that there are no small cuts or holes. Change gloves frequently, and remove immediately after overt contamination. Use care when removing and disposing of gloves in order to minimize exposure.
Skin and body protection	It is recommended that a laboratory coat be worn when handling product.
Hygiene	Wash hands before breaks and immediately after handling the product.

Section IX - PHYSICAL/CHEMICAL CHARACTERISTICS

Appearance	
Physical State	solid
Color	opaque pink
Form	liquid filled gelatin capsule
Other information	
Molecular Weight	Not available
Molecular formula	Not available
Bulk density	Not available
Evaporation rate	Not available
Hydrolysis/Photolysis	Not available
Hygroscopicity	Not available
Log Octanol/Water Partition Coeff [log Kow]	Not available
Surface Tension	Not available
Odor	Not available
Odor Threshold	Not available
pH	Not available
pKa	Not available
Particle Size	Not available

Solubility, Water	Sparingly soluble
Specific Gravity/ Relative density	Not available
Viscosity	solid
Thermal/Stability properties	
Autoignition temperature	Not available
Boiling Point	Not available
Thermal decomposition	Not available
Explosive Limits, LEL	Not available
Explosive limits, UEL	Not available
Explosiveness	Not available
Flammability	Not available
Flash point	Not available
Melting Point	Not available
Oxidizing Potential	Not available
Vapor Properties	
Vapor Density	Not available
Vapor Pressure	negligible
Saturated Vapor Concentration	Not available

Section X - STABILITY AND REACTIVITY

Stability	
Chemical Stability	Not available
Conditions to avoid	Not available
Incompatible products	Not available
Hazardous decomposition products	Hazardous decomposition products: carbon oxides(COx), trace titanium, trace iron oxides
Hazardous reactions	Not available

Section XI - TOXICOLOGICAL INFORMATION

Routes of Entry	Ingestion, Inhalation, Eye contact, Skin contact
Eye Irritation	Glycerol Mildly irritating to eyes.
Skin Irritation	Etoposide Phosphate Possible mild skin irritant. Glycerol Mildly and/or transiently irritating to skin.
Respiratory Irritation	Not available
Sensitization	Etoposide Phosphate Not a dermal sensitizer in an experimental study Glycerol Patch test on human volunteers did not demonstrate sensitization properties.
Acute Toxicity Study	**Acute Oral** Etoposide LD50(rat): 1,784 mg/kg Etoposide Phosphate

	LD50(mouse): 3,800 mg/kg Glycerol LD50(rat): 12,600 mg/kg LD50(mouse): 4,090 mg/kg LD50(rabbit): 27,000 mg/kg LD50(guinea pig): 7,750 mg/kg **Acute Dermal** Glycerol LD50(rat): > 21,900 mg/kg LD50(rabbit): > 10 g/kg **Acute inhalation toxicity** Glycerol LC50(rat): > 570 mg/m3/1 H **Acute toxicity (other routes of administration)** Etoposide Phosphate Maximum nonlethal dose (rat, intravenous): 31 mg/kg LD50 (mouse, intravenous): 147 mg/kg LD50 (mouse, Intraperitoneal): 89 mg/kg
Repeated Dose Toxicity	Etoposide 3 months intravenous (daily) rat study with recovery period (2 months): NOAEL = 0.5 mg/kg (males and females). Microscopic changes were observed in the following organs: testes. No mortality occurred. Etoposide Phosphate 5 D Oral (daily) rat study with recovery period (33 D): NOAEL = 3.44 mg/kg (males and females). Effects include: dehydration, diarrhoea, loose stools, decreased body weight, decreased food consumption, changes in clinical chemistry parameters, decreased organ weights included:, thymus, testes. Microscopic changes were observed in the following organs: bone marrow, thymus, spleen, lymph nodes, small intestine, large intestine, mammary gland, seminal vesicles. No mortality occurred. After recovery, all parameters returned to normal. 20 D Intraperitoneal (5/week) rat study with recovery period (28 D): LOAEL = 12 mg/m2 (males). Effects include: decreased body weight, decreased organ weights included:, testes. 1 months intravenous (daily) rat study with recovery period (1 months): NOAEL = 1.02 mg/m2 (males and females). Effects include: changes in clinical chemistry parameters, bone marrow effects, lymphoid depletion, axonal degeneration, atrophy of the male reproductive organs, injection site reactions, lung inflammation. Microscopic changes were observed in the following organs: lymphatic system, bone marrow, peripheral nervous system, gastrointestinal tract, lungs. Effects still present after recovery include: atrophy of the male reproductive organs, axonal degeneration. 5 D Oral (daily) mouse study with recovery period (30 D): (males and females). Effects include: abnormal posture, dehydration, drooping eyelids, loose stools, hypoactivity, breathing difficulties, decreased body weight, tremors, decrease in body temperature, weakness, collapse,

	death. 20 D Intraperitoneal (5/week) mouse study with recovery period (31 D): LOAEL = 4 mg/kg (males). Effects include: decreased body weight, death. Microscopic changes were observed in the following organs: small intestine, liver, salivary gland, spleen, thymus, bone marrow, testes. 5 D Oral (daily) dog study with recovery period (60 D): NOAEL = 0.975 mg/kg (males and females). Effects include: vomiting, loose stools, dehydration, decreased body weight, decreased food consumption, hypoactivity, changes in clinical pathology parameters. Microscopic changes were observed in the following organs: bone marrow, thymus. After recovery, all parameters returned to normal. Glycerol 90 D Inhalation (5/week) rat study : LOAEL = 0.167 mg/l Microscopic changes were observed in the following organs: throat.
Genetic Toxicity	Etoposide **in vitro** Ames reverse-mutation assay -- positive Mutagenicity (micronucleus test) -- positive Chromosome aberrations assay -- positive **in vivo** Intraperitoneal, Mutagenicity (in vivo mammalian bone-marrow cytogenetic test, chromosomal analysis) (mouse) -- positive Intraperitoneal, mammalian germ cell cytogenetics assay (spermatogonia) (rat) -- positive **Mutagenicity Assessment** This material was positive in a battery of in vivo and in vitro genotoxicity assays. Glycerol **Mutagenicity Assessment** This material was negative in a battery of in vivo and in vitro genotoxicity assays. Not considered a mutagen according to 29 CFR 1910, 67/348/EC or Canadian Controlled Products Regulations.
Carcinogenicity	Etoposide **Carcinogenicity Assessment** The carcinogenic potential has not been studied. Compounds with similar mechanisms of action and mutagenic potential were reported to be carcinogenic. Some secondary cancers developed in persons with other cancers who were treated with this drug, either alone or in combination with other anticancer drugs. It is not known whether these were a result of the treatment with this drug, with one of the other drugs, or a result of progression of the underlying disease. See Human Experience. This material is probably carcinogenic to humans. Glycerol 2 Years Oral rat study : NOAEL = 1,000 mg/kg No treatment-related tumors were observed.

	<table><tr><th>Carcinogenicity</th><th>ACGIH</th><th>OSHA</th><th>NTP</th><th>IARC</th></tr><tr><td>Etoposide</td><td>--</td><td>Listed</td><td>--</td><td>2A</td></tr><tr><td>Etoposide Phosphate</td><td>--</td><td>Listed</td><td>--</td><td>1</td></tr><tr><td>Glycerol</td><td>--</td><td>--</td><td>--</td><td>--</td></tr></table>
Reproductive Toxicity	Etoposide **Assessment Reproductive Toxicity** Animal studies indicate that reproductive effects can occur. See "Human Experience". Glycerol **Assessment Reproductive Toxicity** This substance did not cause adverse effects on male or female reproduction or on the offspring of treated animals.
Developmental Toxicity	Etoposide **Developmental Toxicity Assessment** This material has been shown to cross the placenta. Birth defects were observed in animal studies. This compound and/or its metabolites may be excreted into the milk. See "Human Experience". Glycerol **Developmental Toxicity Assessment** Several developmental studies were conducted. Did not show teratogenic effects in animal experiments. This material has been shown to cross the placenta.
Human experience	**Clinical Trials** Glycerol 50 D Oral route, healthy volunteers 1,300 - 2,200 mg/kg - No significant adverse effects were observed. **Experiences with Human Exposure** Etoposide General effects therapeutic use - Symptoms: nausea, vomiting, diarrhoea, loss of appetite, abdominal pain, chest pain, heart attack, congestive heart failure, hair loss, rash, nail changes, menstrual irregularities, asthma, breathing difficulties, difficulty swallowing, bruising, confusion, skin effects, eye effects, fatigue, headache, impairment of vision, tingling, numbness, pain. Other effects include: colitis, acute leukemia, lowered blood pressure, changes in blood clotting parameters, cardiac irregularities, inflammation of gastrointestinal tract, decreased red blood cell count, decreased white blood cell count, anaphylaxis, liver toxicity, peripheral neuropathies, ovarian changes, sperm abnormalities. Glycerol General effects therapeutic use - Symptoms: headache, dizziness, nausea, vomiting, thirst, diarrhoea, confusion, dry mouth, eye irritation. Other effects include: changes in red blood cell parameters, kidney disorders, other central nervous effects, increased urine volume, cardiac irregularities, hyperglycemia, electrolyte disturbance, coma. This substance has laxative effects. This substance has strong osmotic effects.
Target Organs	Etoposide bone marrow, gastrointestinal tract, peripheral nervous system,

	lymphatic system, cardiovascular system, female reproductive organs, male reproductive organs Glycerol gastrointestinal tract
Symptoms	Etoposide See "Human Experience". Glycerol See "Human Experience".
Other Toxicity Information	Not available

Section XII - ECOLOGICAL INFORMATION

Ecotoxicological Information (Aquatic)
Acute Toxicity to Fish
Glycerol
LC50 (Oncorhynchus mykiss (rainbow trout), 96 H) : 51,000 - 57,000 mg/l.
Acute Toxicity to Aquatic Invertebrates
Etoposide Phosphate
EC50 (Daphnia magna (Water flea)) : > 61.8 mg/l.
Glycerol
EC50 (Daphnia magna (Water flea), 24 H) : > 500 mg/l.
Toxicity to microorganisms
Etoposide Phosphate
Respiration inhibition, EC50 (Activated Sludge) : 19.5 mg/l

Ecotoxicological Information (Terrestrial) Not available

Chemical fate information
Biodegradation
Etoposide Phosphate
Readily biodegradable.

Glycerol
Ready biodegradation (14 D) : 63 % ; Readily biodegradable - rapidly biodegrades in the environment

Stability in water
Etoposide Phosphate
Half-life - 11.3 H

Summary Statements
Aquatic toxicity
Glycerol
Experimental data indicate low potential for acute harm to aquatic organisms.

Section XIII - DISPOSAL INFORMATION

Advice on Disposal And Packaging: Disposal should be in accordance with applicable regional, national and local laws and regulations. Local regulations may be more stringent than regional or national requirements. This information presented only applies to the material as supplied.

Section XIV - TRANSPORTATION INFORMATION

This material is not a dangerous good for the purpose of transportation.

Section XV - REGULATORY INFORMATION

United States of America	
OSHA Hazard Classification	Mutagen Carcinogen Reproductive toxicant developmental toxicant Target Organs
313 Toxic Release Inventory. Listed Chemicals/Compounds	No components listed on the SARA 313 inventory.
TSCA Inventory	Not listed. Food, drug and cosmetic products are exempt from TSCA.
California Prop. 65	developmental toxicant Etoposide
International	
Canada	
WHMIS	Finished medicinal products are not classified under WHMIS, but using the classification criteria this material would be considered: D2A Very Toxic Material Causing Other Toxic Effects D2B Toxic Material Causing Other Toxic Effects
DSL/NDSL	Not listed.
Mexico	
Mexico Classification	Health classification - Serious Hazard - 3 - Substances that can cause serious or permanent harm under emergency conditions
Europe	
EINECS/ELINCS/Registration Number	Etoposide: 251-509-1 Glycerol: 200-289-5 Gelatin: 232-554-6 Water: 231-791-2 Citric Acid: 201-069-1 Sodium propyl-4-hydroxybenzoate: 252-488-1 Sodium ethyl-4-hydroxybenzoate: 252-487-6 Red Iron Oxide: 215-168-2 Titanium Dioxide: 236-675-5
Other information	Medicinal products are exempt from classification and labelling requirements under EU Preparations Directive 1999/45/EC.

Section XVI - OTHER DATA

MSDS preparation information	
Prepared on	21/03/2017
	This Safety Data Sheet has been revised. This MSDS has been reformatted in a new electronic system.
Other information	
HMIS	<table><tr><td>Health</td><td>1</td></tr><tr><td>Flammability</td><td>1</td></tr></table>

	Reactivity	Not Determined (ND)
	Personal protective equipment	See Section 8.
NFPA	Health 1 Fire 1 Reactivity ND Special ND	
The information contained in this MSDS is believed to be accurate and represents the best information reasonably available at the time of preparation. However, we make no warranty, express or implied, with respect to such information. and we assume no liability from its use.		