OVERDOSAGE
There is no known antidote for overdoses of vinorelbine. If overdosage occurs, general supportive measures together with appropriate blood transfusions, growth factors, and antibiotics should be instituted as deemed necessary.

DIRECTIONS:
Store between 2°C-8°C. Donot Freeze. Protect from light. To be sold on prescription only.

PRESENTATION
VINOTEC-10 is available as 10mg/1ml in a vial with a package insert.
VINOTEC-50 is available as 50mg/5ml in a vial with a package insert.

Marketed by:
Revive healthcare
503, 5th Floor, Eden Heights, 6 Main Gulberg, Jail Road, Lahore - Pakistan 54600.

Manufactured by:
United Biotech (P) Limited
Bagbania, Baddi-Nalagarh Road, Distt. Solan (HP) - 174 101 - India

وینوٹیک
(وینوریلبین)
۵۰ ملی گرام/۵ ملی لیٹر

دوا کو صرف ڈاکٹری نسخے کے ذریعہ ہی فروخت کریں۔
دوا کو روشنی سے محفوظ رکھیں اور بچوں سے دور رکھیں۔
ڈاکٹری ہدایت کے مطابق استعمال کریں۔
بچوں کی پہنچ سے دور رکھیں۔

Rx Vinorelbine Injection 10mg/1ml & 50mg/5ml

VINOTEC 10/50 mg

For I.V. use only

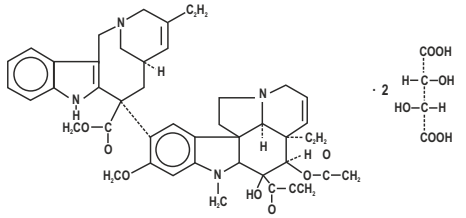
PHARMACEUTICALS WORLDWIDE
UNITED BIOTECH
The Emergence of a New Standard

WARNINGS
Caution : FATAL IF GIVEN INTRATHECALLY.

COMPOSITION
Each Vial of 5ml contains:
Vinorebine tartrate eq. to Vinorelbine 50mg
(U.S.P. Specs.)

DESCRIPTION
Vinorelbine is a semisynthetic vinca alkaloid with antitumour activity.It is a derivative of vinblastine and has structural modifications distinctly different from other vinca alkaloids and a spectrum of activity similar to either vincristine or vinblastine.The chemical name is 3',4'-didehydro-4'-deoxy-C'-norvincaleukoblastine [R-(R*,R*)-2,3-dihydroxybutanedi- oate (1:2)(salt)]. Vinorelbine tartrate has the following structure:

Vinorelbine tartrate is a white to yellow or light brown amorphous powder with the molecular formula $C_{45}H_{54}N_4O_8 \cdot 2C_4H_6O_6$ and molecular weight of 1079.12. The aqueous solubility is >1,000 mg/mL in distilled water. The pH of Vinorelbine Injection is approximately 3.5.



CLINICAL PHARMACOLOGY
Following intravenous administration, vinorelbine concentration in plasma decays in a triphasic manner.The initial rapid decline primarily represents distribution of drug to peripheral compartments followed by metabolism and excretion of the drug during subsequent phases.The prolonged terminal phase is due to relatively slow efflux of vinorelbine from peripheral compartments. Elimination occurs through bile (34-58%) and renal (16-21%) routes. Two-thirds of renal elimination happens in the first 24 hours.The terminal phase half-life averages 27.7 to 43.6 hours and the mean plasma clearance ranges from 0.97 to 1.26 L/hr/kg. Steady-state volume of distribution (V_{ss}) values range from 25.4 to 40.1 L/kg. Vinorelbine demonstrated high binding to human platelets and lymphocytes. The free fraction was approximately 0.11 in pooled human plasma over a concentration range of 234 to 1,169 ng/mL. The binding to plasma constituents in cancer patients ranged from 79.6% to 91.2%. Vinorelbine binding was not altered in the presence of cisplatin, 5-fluorouracil, or doxorubicin.

Vinorelbine undergoes substantial hepatic elimination in humans, with large amounts recovered in feces after intravenous administration to humans. Two metabolites of vinorelbine have been identified in human blood, plasma, and urine; vinorelbine N-oxide and deacetylvinorelbine. Approximately 18% and 46% of the administered dose was recovered in the urine and in the feces, respectively.

INDICATIONS
Vinorelbine Injection is indicated either alone or in combination with cisplatin for the first-line treatment of ambulatory patients with unresectable, advanced non-small cell lung carcinoma. In patients with Stage IV advanced non-small cell lung carcinoma Vinorelbine is indicated as a single agent or in combination with cisplatin. In Stage III non-small cell lung carcinoma Vinorelbine is indicated in combination with cisplatin.

DOSAGE AND ADMINISTRATION

Non-small cell lung cancer

Adults:

Single agent therapy: 30mg/m^2 administered over 6 to 10 minutes once weekly.

Combination therapy with Cisplatin:

Usual dosage: 25mg/m^2 administered IV once weekly in combination with cisplatin 100mg/m^2 every 4 weeks.

Alternative dosage: 30mg/m^2 administered IV once weekly in combination with cisplatin 120mg/m^2 given on days 1 and 29 then every 6 weeks.

Preparation for Solution: Vinorelbine Injection must be diluted in a syringe or IV bag using one of the recommended solutions.

Dilution in a syringe: The calculated dose of vinorelbine should be diluted to a concentration between 1.5 and 3.0 mg/ml using one of the following solutions: 5% dextrose; 0.9% Nacl Injection.

For an IV Infusion: The calculated dose of vinorelbine should be diluted to a concentration between 0.5 and 2 mg/ml using one of the following: 5% Dextrose; 0.9% NaCl Injection I.P. or Ringer Lactate. Inject the diluted injection over 6-10 minutes via Y-site into a free flowing IV infusion closest to the IV bag. After injection, flush with at least 75-125 ml of any of the above solution used for dilution.

For other uses

Dose Modifications: The dosage should be adjusted according to hematologic toxicity or hepatic insufficiency.

Dose Modifications for Hematologic Toxicity: Granulocyte counts should be 1,000 cells/mm^3 prior to the administration. Adjustments in the dosage should be based on granulocyte counts obtained on the day of treatment according to below given Table.

Dose Adjustments Based on Granulocyte Counts	
Granulocytes on Day of Treatment (cells/mm^3)	Percentage of Starting Dose
≥1,500	100%
1,000 to 1,499	50%
<1,000	Do not administer. Repeat granulocyte count in 1 week. If 3 consecutive weekly doses are held because granulocyte count is <1,000 cells/mm^3, discountinue Vinorelbine.
Note : For patients who, during treatment, experienced fever and/or sepsis while granulocytopenic and had 2 consecutive weekly doses held due to granulocytopenia, subsequent doses of Vinorelbine should be :	
≥1,500	75%
1,000 to 1,499	37.5%
<1,000	See Above

Dose Modifications for Hepatic Insufficiency: Vinorelbine should be administered with caution to patients with hepatic insufficiency. In patients who develop hyperbilirubinemia during treatment , the dose should be adjusted for total bilirubin according to the below given table.

Dose Modification Based on Total Bilirubin	
Total Bilirubin (mg/dL)	**Percentage of Starting Dose**
≤2.0	100%
2.1 to 3.0	50%
>3.0	25%

Dose Modifications for Concurrent Hematologic Toxicity and Hepatic Insufficiency: In patients with both hematologic toxicity and hepatic insufficiency, the lower of the doses based on the corresponding starting dose determined from the above two tables should be administered.

Dose Modifications for Renal Insufficiency: No dose adjustments are required for renal insufficiency. Appropriate dose reductions for cisplatin should be made when used in combination with Vinorelbine.

Dose Modifications for Neurotoxicity: If Grade ≥ 2 neurotoxicity develops, Vinorelbine should be discontinued.

CONTRAINDICATIONS

It is contraindicated in patients with pretreatment granulocyte counts <1000 cells/mm^3 and those hypersensitive to Vinorelbine.

DRUG INTERACTIONS

Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP3A subfamily, or in patients with hepatic dysfunction. Concurrent administration of vinorelbine tartrate with an inhibitor of this metabolic pathway may cause an earlier onset and/or an increased severity of side effects. Acute pulmonary reactions have been reported when used in conjunction with mitomycin. The incidence of granulocytopenia is significantly higher on concurrent administration of cisplatin than single agent Vinorelbine. Patients who receive Vinorelbine and Paclitaxel, either concomitantly or sequentially, should be monitored for signs and symptoms of neuropathy. Patients with prior or concomitant radiation therapy may result in radiosensitizing effects.

ADVERSE REACTIONS

Hematologic Toxicity: Granulocytopenia is the major dose-limiting toxicity. It occurs in 2/3rd of the patients. Dose adjustments are required for hematologic toxicity and hepatic insufficiency. Granulocytopenia was generally reversible and not cumulative over time.

Non-hematological toxicities: Nausea, vomiting (usually controlled with standard antiemetics), constipation, peripheral neuropathy weakness, alopecia, and pain at the injection site (Table).

Adverse Experience	All Grades		Grade III		Grade IV	
	n	(%)	n	(%)	n	(%)
Nausea/Vomiting	1607	(30)	30	(1.9)	5	(0.3)
Constipation	1027	(24)	27	(2.0)	9	(0.7)
PeripheralNeuropathy	375	(23)	42	(2.6)	2	(0.1)
Cardiac	39	(2.6)	4	(0.3)	5	(0.3)
Alopecia	352	(25)	57	(4.1)	0	(0)
Injection-site reaction	358	(2.6)	53	(3.6)	2	(0.1)
Infection	204	(13)	26	(1.6)	20	(1.2)

n = number of affected patients

Neurologic: Less than 5% of the patients experienced loss of deep tendon reflexes. The development of severe peripheral neuropathy was infrequent (1%) and generally reversible.

Skin: Injection site reactions, including erythema, pain at injection site, and vein discoloration, occurred in approximately one third of patients of which 5% of them were severe. Chemical phlebitis along the vein proximal to the site of injection was reported in 10% of patients.

Gastrointestinal: Due to the low incidence of severe nausea and vomiting on administration of Vinorelbine as a single-agent the use of serotonin antagonists is generally not required.

Hepatic: Transient elevations of liver enzymes were reported without clinical symptoms.

Cardiovascular: Chest pain was reported in 5% of patients. Most reports of chest pain were in patients who had either a history of cardiovascular disease or tumor within the chest. There have been rare reports of myocardial infarction.

Pulmonary: 3% of the patients reported shortness of breath in 2% it was severe.

Other: Fatigue occurred in 27% of patients. It was usually mild or moderate but increased with cumulative dosing. Other toxicities that have been reported in less than 5% of patients include jaw pain, myalgia, arthralgia, and rash. Hemorrhagic cystitis and the syndrome of inappropriate ADH secretion were each reported in <1% of patients.

WARNING AND PRECAUTIONS

1. Vinorelbine should not be administered to patients with granulocyte counts <1,000 cells/mm^3. Patients developing severe granulocytopenia should be monitored carefully for evidence of infection and/or fever.
2. Pregnancy : Pregnancy Category D. Vinorelbine may cause fetal harm if administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with Vinorelbine.
3. Caution should be exercised when administering Vinorelbine to patients with severe hepatic injury or impairment.
4. Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenic potential of Vinorelbine has not been studied. Vinorelbine has been shown to affect chromosome number and possibly structure in vivo (polyploidy in bone marrow cells from Chinese hamsters and a positive micronucleus test in mice). It was not mutagenic in the Ames test and gave inconclusive results in the mouse lymphoma TK Locus assay. The significance of these or other short-term test results for human risk is unknown. Vinorelbine does not affect fertility to a statistically extent when administered to rats on either a once-weekly (9 mg/m^2, approximately 1/3rd the human dose) or alternate-day schedule (4.2 mg/m^2, approximately 1/7th the human dose) prior to and during mating. However, biweekly administration for 13 or 26 weeks in the rat at 2.1 and 7.2 mg/m^2 (approximately 1/15th and 1/4th the human dose) result in decreased spermatogenesis and prostate/seminal vesicle secretion.
5. Nursing Mothers : It is recommended that nursing be discontinued in women who are being treated with Vinorelbine.
6. Pediatric Use : Safety and effectiveness of Vinorelbine in pediatric patients have not been established.
7. Geriatric Use: No overall differences in effectiveness or safety were observed between these patients and younger adult patients.