141.0 mm

206.0 mm

50mg/5ml Injection

VINOBIN

(V I N O R E L B I N E)

۵۰ ملی گرام/۵ ملی لیٹر انجکشن

وینوبین

(وینورلبین)

COMPOSITION

Each 5ml contains:

Vinorelbine as tartrate…….....50mg

(USP Specifications)

DESCRIPTION

Vinorelbine is an anti-mitotic chemotherapy drug that is used in the treatment of several types of malignancies, including breast cancer and non-small cell lung cancer (NSCLC). It was initially approved in the USA in 1990's for the treatment of NSCLC.

It is a third-generation vinca alkaloid. The introduction of third-generation drugs (vinorelbine, gemcitabine, taxanes) in platinum combination improved survival of patients with advanced NSCLC, with very similar results from the various drugs.

MECHANISM OF ACTION

Vinorelbine inhibits tubulin polymerization and binds preferentially to mitotic microtubules, only affecting axonal microtubules at high concentrations. Spiralisation of the tubulin is induced to a lesser degree than with vincristine. Vinorelbine blocks mitosis in phase G2-M, causing cell death in interphase or at the following mitosis.

Vinorelbine is an antineoplastic active substance of the vinca alkaloid family, but in contrast to all other vinca alkaloids the catharanthine portion of vinorelbine has undergone a structural modification. On the molecular level it affects the dynamic equilibrium of tubulin in the microtubular system of the cell.

INDICATIONS

Vinorelbine is indicated:

- In combination with cisplatin for first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC)
- As a single agent for the treatment of patients with metastatic NSCLC.
- Treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen.

DOSAGE & ADMINISTRATION

Vinorelbine is usually given at 25-30 mg/m^2 once weekly.

In combination with other cytostatic agents the exact dose should be taken from the treatment protocol. i.e

In Combination with Cisplatin 100 mg/m^2

The recommended dosage of Vinorelbine is 25mg/m^2 administered as an intravenous injection or infusion over 6 to 10 minutes on Days 1, 8, 15 and 22 of a 28-day cycle in combination with cisplatin 100 mg/m^2 on Day 1 only of each 28-day cycle.

In Combination with Cisplatin 120 mg/m^2

The recommended dosage of Vinorelbine is 30 mg/m^2 administered as an intravenous injection or infusion over 6 to 10 minutes once a week in combination with cisplatin 120 mg/m^2 on Days 1 and 29, then every 6 weeks.

Vinorelbine may be administered by slow bolus (6-10 minutes) after dilution in 20-50 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection or in 5 % (w/v) glucose solution for injection or by a short infusion (20-30 minutes) after dilution in 125 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection or in 5 % (w/v) glucose solution for injection. Administration should always be followed by a sodium chloride 9 mg/ml (0.9 %) infusion with at least 250 ml to flush the vein.

The maximum tolerated dose per administration: 35.4 mg/m^2 body surface area

The maximum total dose per administration: 60 mg

Dose modifications

Vinorelbine metabolism and clearance are mostly hepatic: only 18.5 % is excreted unchanged in the urine. No prospective study relating altered metabolism of the active substance to its pharmacodynamic effects is available in order to establish guidelines for vinorelbine dose reduction in patients with impaired liver or kidney function.

Myelosuppression

Hold or decrease the dose of Vinorelbine in patients with decreased neutrophil counts according to the following:

Neutrophils on Day of Treatment (cells/mm^3)	Percentage of Starting Dose of Vinorelbine
≥ 1,500	100%
1,000 to 1,499	50%
< 1,000	Do not administer Vinorelbine . Repeat neutrophil count in one week. If three consecutive weekly doses are held because neutrophil count is < 1,000 cells/mm3 , discontinue Vinorelbine
Note: For patients who experience fever and/or sepsis while neutrophil count is < 1,500 cells/mm3 or had 2 consecutive weekly doses held due to neutropenia, subsequent doses of Vinorelbine should be	
> 1,500	75%
1,000 to 1,499	37.5%
< 1,000	Do not administer Vinorelbine. Repeat neutrophil count in one week.

Hepatic impairment

The pharmacokinetics of vinorelbine is not modified in patients presenting moderate or severe liver impairment.

Nevertheless as a precautionary measure a reduced dose of 20 mg/m2 and close monitoring of haematological parameters is recommended in patients with severe liver.

Renal impairment

Given the minor renal excretion, there is no pharmacokinetic rationale for reducing vinorelbine dose in patients with impaired kidney function.

Elderly

Clinical experience has not detected any significant differences among elderly patients with regard to the response rate, although greater sensitivity in some of these patients cannot be excluded. Age does not modify the pharmacokinetics of vinorelbine (see section 5.2).

Pediatric population

The safety and efficacy in children have not been established and administration is therefore not recommended.

Method of administration

Strictly intravenous administration after appropriate dilution.

Intrathecal administration of vinorelbine may be fatal.

Preparation

Dilute VINORELBINE in an intravenous bag to a concentration between 0.5 mg/mL and 2 mg/ml. Use one of the following recommended solutions for dilution:

- 5% Dextrose Injection, USP
- 0.9% Sodium Chloride Injection, USP
- 0.45% Sodium Chloride Injection, USP
- 5% Dextrose and 0.45% Sodium Chloride Injection, USP
- Ringer's Injection, USP
- Lactated Ringer's Injection, USP

Stability and Storage Conditions of Diluted Solutions

Diluted Vinorelbine may be used for up to 24 hours under normal room

light when stored in polyvinyl chloride bags at 5° to 30°C (41° to 86°F).

Administration

Administer diluted Vinorelbine over 6 to 10 minutes into the side port of a free-flowing intravenous line followed by flushing with at least 75 to 125 mL of one of the solutions. **Vinorelbine must only be administered intravenously.** It is extremely important that the intravenous needle or catheter be properly positioned before any Vinorelbine is injected. Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. If particulate matter is seen, Vinorelbine should not be administered.

Management of Suspected Extravasation

If Vinorelbine leakage into surrounding tissue occurs or is suspected, immediately stop administration of Vinorelbine and initiate appropriate management measures in accordance with institutional policies.

Procedures for Proper Handling and Disposal

Vinorelbine is a cytotoxic drug. Follow applicable special handling and disposal procedures. Exercise caution in handling and preparing the solution of Vinorelbine. The use of gloves is recommended. If the solution of Vinorelbine contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water. Avoid contamination of the eye with VINORELBINE. If exposure occurs, flush the eyes with water immediately and thoroughly. Discard unused portion.

PHARMACOKINETICS

The pharmacokinetics of vinorelbine were studied in 49 patients who received doses of 30 mg/m2 administered as 15- to 20-minute constant-rate infusions. Vinorelbine concentrations in plasma decay in a triphasic manner.

Distribution

Steady-state volume of distribution (VSS) 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 human plasma over a concentration range of 234 to 1169 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, fluorouracil, or doxorubicin. Elimination 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.

Metabolism

Vinorelbine undergoes substantial hepatic elimination in humans, with large amounts recovered in feces. Two metabolites of vinorelbine have been identified in human blood, plasma and urine; vinorelbine N-oxide and deacetylvinorelbine. Deacetylvinorelbine has been demonstrated to be the primary metabolite of vinorelbine in humans and has been shown to possess antitumor activity similar to vinorelbine. Therapeutic doses of vinorelbine (30 mg/m2) yield very small, if any, quantifiable levels of either metabolite in blood or urine. The metabolism of vinorelbine is mediated by hepatic CYP3A.

Excretion

After intravenous administration of radioactive vinorelbine, approximately 18% and 46% of administered radioactivity was recovered in urine and feces, respectively. In a different study, 10.9% ± 0.7% of a 30 mg/m2 intravenous dose was excreted as parent drug in urine.

WARNINGS AND PRECAUTIONS

Special warnings

• Vinorelbine should be administered under the supervision of a physician experienced in the use of chemotherapy.

• Vinorelbine must only be administered by the intravenous route. The use of intrathecal route is contra-indicated. Administration should always be followed by a sodium chloride 9 mg/ml (0.9 %) infusion to flush the vein.

Vinorelbine must be administered intravenously with great precision:

• It is very important to make sure that the cannula has been accurately placed into the vein before starting to infuse vinorelbine. If vinorelbine extravasates during intravenous administration, this can cause considerable local irritation. In this case, the infusion must be stopped immediately, the vein flushed through with sodium chloride 9 mg/ml (0.9 %) solution and the rest of the dose should be administered in another vein. Additionally, published data support the use of treatment with hyaluronidase and dry heat in the event of extravasation. Consultation of a plastic surgeon at early stages of necrosis or compartment-syndrome, persistent or progressive pain or failure of conservative treatment is recommended.

• Treatment should be undertaken with close haematological monitoring (determination of haemoglobin level and number of leukocytes, granulocytes and thrombocytes before each new injection). The dose-limiting adverse reaction is mainly neutropenia. This effect is non-cumulative, having its nadir between 7 and 14 days after the administration and is rapidly reversible within 5 to 7 days. If the neutrophil count is <1,500/mm3 and/or thrombocyte count is below 100,000/mm3, treatment should be delayed until recovery and the patient should be observed. Administration of the medicinal product is expected to be delayed by 1 week in about 35 % of treatment courses.

• If patients present signs or symptoms suggestive of infection, a prompt investigation should be carried out.

• Interstitial lung disease has been reported more frequently in the Japanese population. Special attention should be exercised for this specific population.

Myelosuppression

Myelosuppression, manifested by neutropenia, anemia and thrombocytopenia, occur in patients receiving VINORELBINE as a single agent and in combination with cisplatin. Neutropenia is the major dose-limiting toxicity with VINORELBINE. Grade 3-4 neutropenia occurred in 53% of patients treated with VINORELBINE at 30 mg/m^2 per week. Dose adjustment due to myelosuppression occurred in 51% of patients. Monitor complete blood counts prior to each dose of VINORELBINE. Do not administer VINORELBINE to patients with neutrophil counts.

Hepatic Toxicity

Drug-induced liver injury manifest by elevated aspartate aminotransferase (AST) and bilirubin occur in patients receiving VINORELBINE as a single agent and in combination with cytotoxic agents. Assess hepatic function prior to initiation of VINORELBINE and periodically during treatment. Reduce the dose of VINORELBINE for patients who develop elevations in total bilirubin > 2 times upper limit of normal.

Severe Constipation and Bowel Obstruction

Severe and fatal paralytic ileus, constipation, intestinal obstruction, necrosis, and perforation occur in patients receiving VINORELBINE. Institute a prophylactic bowel regimen to mitigate potential constipation, bowel obstruction and/or paralytic ileus, considering adequate dietary fiber intake, hydration and routine use of stool softeners.

Extravasation and Tissue Injury

Extravasation of VINORELBINE can result in severe irritation, local tissue necrosis and/or thrombophlebitis. If signs or symptoms of extravasation occur, immediately stop administration of VINORELBINE and institute recommended management procedures.

Neurologic Toxicity

Sensory and motor neuropathies, including severe neuropathies, occur in patients receiving VINORELBINE. Monitor patients for new or worsening signs and symptoms of neuropathy, such as paresthesia, hyperesthesia, hyporeflexia and muscle weakness while receiving VINORELBINE. Discontinue VINORELBINE for CTCAE Grade 2 or greater neuropathy.

Pulmonary Toxicity and Respiratory Failure

Pulmonary toxicity, including severe acute bronchospasm, interstitial

pneumonitis, acute respiratory distress syndrome (ARDS) occur in patients receiving VINORELBINE. Interstitial pneumonitis and ARDS included fatalities. The mean time to onset of interstitial pneumonitis and ARDS after vinorelbine administration was one week (range 3 to 8 days). Interrupt VINORELBINE in patients who develop unexplained dyspnea or have any evidence of pulmonary toxicity. Permanently discontinue VINORELBINE for confirmed interstitial pneumonitis or ARDS.

Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, VINORELBINE can cause fetal harm when administered to a pregnant woman. In animal reproduction studies in mice and rabbits, embryo and fetal toxicity were observed with administration of vinorelbine at doses approximately 0.33 and 0.18 times the human therapeutic dose, respectively. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with VINORELBINE and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with VINORELBINE and for 3 months after the final dose

Special precautions for use

If there is significant hepatic impairment the dose should be reduced: caution is recommended and careful monitoring of haematological parameters required.

- In case of renal impairment, because of the low level of renal excretion, no dose modification is necessary.
- Vinorelbine should not be given concomitantly with radiotherapy if the treatment field includes the liver.
- Strong CYP3A4- inhibitors or inducers should be administered with caution because of the risk of affecting the vinorelbine concentration.
- This product is generally not recommended in combination with itraconazole (like all vinca alkaloids) and phenytoin (like all cytotoxic).
- This product is specifically contraindicated with yellow fever vaccine and its concomitant use with other live attenuated vaccines is not recommended.
- To avoid bronchospasm – especially if used concomitantly with mitomycin C-appropriate precautionary measures should be considered. Patients treated on an outpatient basis should be informed that they should contact the physician in case of dyspnoea.
- It is recommended that special caution should be shown towards patients with ischemic heart disease in the medical history.
- All contact with the eyes should be strictly avoided: risk of severe irritation and even corneal ulceration if the medicinal product is sprayed under pressure. Immediate liberal washing of the eye with sodium chloride 9 mg/ml (0.9 %) solution should be undertaken if any contact occurs.

Pregnancy

Vinorelbine is contraindicated during pregnancy. Women should not become pregnant during treatment with vinorelbine.

In case of a vital indication a medical consultation concerning the risk of harmful effects for the child should be performed for the therapy of a pregnant patient.

If pregnancy occurs during the treatment, the possibility of genetic counselling should be considered.

Women of childbearing potential

Women of childbearing potential must be advised to use effective contraception during and up to three months after treatment and to inform their doctor if they become pregnant.

Breast-feeding

It is unknown whether vinorelbine is excreted in human milk. The excretion of vinorelbine in milk has not been studied in animals. A risk to the newborns/infants cannot be excluded. Breast-feeding must be discontinued before starting treatment with vinorelbine (see section 4.3).

Fertility

Men being treated with vinorelbine are advised not to father a child during and up to 6 months after treatment. Prior to treatment advice should be sought for conserving sperm due to the risk of irreversible infertility as a consequence of treatment with vinorelbine.

206.0 mm

SIDE EFFECTS

Organ / systems	Adverse reactions
infections and infestations	Common Infection bacterial, viral or fungal at different localisation (respiratory, urinary, GI tract) mild to moderate and usually reversible with an appropriate treatment. Uncommon Severe sepsis with other visceral failure, septicaemia. Very rare Septicaemia complicated; septicaemia fatal. Not known Neutropenic sepsis (with potential fatal outcome in 1.2 % of cases).
Blood and lymphatic system disorders	Very common Bone marrow depression resulting mainly in neutropenia (G3: 24.3 % and G4: 27.8 % in monotherapy) reversible within 5 to 7 days and non -cumulative over time, anaemia (G3 -4: 7.4 % in monotherapy). Common Thrombocytopenia (G3 -4: 2.5 %) may occur but is seldom severe. No t known Febrile neutropenia, pancytopenia.
Immune system disorders	Common Allergic reactions (skin reactions, respiratory reactions). Not known Systemic allergic reactions (anaphylactic reaction or shock, anaphylactoid reaction, angioedema).
Endocrine disorders	Not known Inappropriate antidiuretic hormone secretion (SIADH).
Metabolism and nutrition disorders	Rare Severe hyponatraemia. Not known Anorexia.
Nervous system disorders	Very common Neurological disorders (G3: 2.6 %; G4: 0.1 %) including loss of deep tendon reflexes. Weakness of the lower extremities has been reported after a prolonged chemotherapy. Uncommon Severe paraesthesia with sensory and motor symptoms. These effects are generally reversible. Very rare Guillain Barré syndrome
Cardiac disorders	Rare Ischaemic heart diseases like angina pectoris, transitory electrocardiogram changes, myocardial infarction, sometimes fatal. Very rare Tachycardia, palpitation and heart rhythm disorders.
Vascular disorders	Uncommon Hypotension, hypertension, flushing and peripheral coldness Rare Severe hypotension, collapse.
Respiratory, thoracic and mediastinal disorders	Uncommon Dyspnoea and bronchospasm may occur in association with vinorelbine treatment as with other vinca alkaloids. Rare Interstitial lung disease, sometimes fatal has been reported. Very rare Respiratory insufficiency.
Gastrointestinal disorders	Very common Constipation is the main symptom (G 3-4: 2.7 %) which rarely progresses to paralytic ileus with vinorelbine as single agent (G3-4: 4.1 %) and with the combination of vinorelbine and other chemotherapeutic agents. Nausea and vomiting (G1-2: 30.4 %, G3-4: 2.2 % in monotherapy; antiemetic therapy may reduce their occurrence), stomatitis (G1-4: 15 % in monotherapy), oesophagitis. Common Diarrhoea (usually mild to moderate). Rare Paralytic ileus; treatment may be resumed after recovery of normal bowel mobility, pancreatitis
Hepatobiliary disorders	Very common Transient elevations of liver function tests (G1-2) without clinical symptoms were reported (total bilirubin increased, alkaline phosphatase increased, aspartate aminotransferase increased in 27.6 %, alanine aminotransferase increased in 29.3 %).
Skin and subcutaneous tissue disorders	Very common Alopecia usually mild in nature (G3-4: 4.1 % in monotherapy). Rare Generalised cutaneous reactions. Not known : Palmar -plantar erythrodysesthesia syndrome.
Musculoskeletal and connective tissue disorders	Common Myalgia, arthralgia, jaw pain.
Renal and urinary disorders	Common Creatinine increased.
General disorders and administration site conditions	Very common Asthenia, fatigue, fever, pain in different locations including chest pain and pain at the tumour site. Reactions at the injection site may include erythema, burning pain, vein discolouration and local phlebitis (G3-4: 3.7 % with vinorelbine as single chemotherapeutic agent). Rare Injection site necrosis (proper positioning of the intravenous needle or catheter and bolus injection followed by liberal flushing of the vein can limit these effects).

141.0 mm

206.0 mm

DRUG INTERACTIONS

Interactions common to all cytotoxics

Due to the increase of thrombotic risk in case of tumoural diseases, the use of anticoagulative treatment is frequent. If the patient receives anticoagulative treatment the frequency of INR (International Normalised Ratio) monitoring should be increased, due to high intra-individual variability of the coagulability during diseases, and the eventuality of interaction between oral anticoagulants and anticancer chemotherapy.

Concomitant use not recommended

This product is generally not recommended in combination with live attenuated vaccines because of the risk of generalised, possibly fatal vaccine disease. This risk is increased in patients already immunodepressed by their underlying disease. It is recommended to use an inactivated vaccine when exists (poliomyelitis)

Concomitant use contraindicated

For yellow fever vaccine the concomitant use is contraindicated.

Phenytoin: risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by the cytotoxic medicinal product or risk of toxicity enhancement or loss of efficacy of the cytotoxic medicinal product due to increased hepatic metabolism by phenytoin.

Concomitant use to take into consideration

Cyclosporine, tacrolimus: Excessive immunosuppression with risk of lymphoproliferation is to be taken into consideration.

Interactions specific to vinca alkaloids

Concomitant use not recommended

Itraconazole should not be administered concomitantly because of the risk of increased neurotoxicity due to the decrease of their hepatic metabolism.

Concomitant use to take into consideration

Concomitant use of vinca alkaloids and mitomycin C increases the risk of bronchospasm and dyspnoea. In rare cases, particularly in combination with mitomycin, an interstitial pneumonitis was observed.

Vinorelbine is a P-glycoprotein substrate and concomitant use with inhibitors (e.g. verapamil, ciclosporin and quinidine) or inducers of this transport protein can affect the concentration of vinorelbine.

Interactions specific to vinorelbine

The combination of vinorelbine with other medicinal products with known bone marrow toxicity is likely to exacerbate the myelosuppressive adverse reactions.

As CYP 3A4 is mainly involved in the metabolism of vinorelbine, combination with strong inhibitors of this isoenzyme (e.g. itraconazole, ketoconazole, clarithromycin, erythromycin and ritonavir) could increase blood concentrations of vinorelbine and combination with strong inducers of this isoenzyme (e.g. rifampicin, phenytoin, phenobarbital, carbamazepin and St. John's wort) could decrease blood concentrations of vinorelbine.

The combination of vinorelbine and cisplatin (a very common combination) does not affect the pharmacokinetic parameters. However, there is higher incidence of granulocytopenia in the combination of vinorelbine and cisplatin than in vinorelbine as monotherapy.

An increased incidence of grade 3/4 neutropenia has been suggested when intravenous vinorelbine and lapatinib were associated in one clinical phase I study. In this study, the recommended dose of intravenous form of vinorelbine in a 3-weekly schedule on day 1 and day 8 was 22.5 mg/m2 when combined with daily lapatinib 1000 mg. This type of combination should be administered with caution.

OVERDOSE

Cases of accidental acute overdose have been reported in humans: Such cases can result in bone marrow hypoplasia and are sometimes associated with infection, fever and paralytic ileus. Supporting treatment such as blood transfusion, growth factors or broad-spectrum antibiotic treatment is normally initiated at the doctor's discretion. There is no known antidote.

As there is no specific antidote for the overdose of vinorelbine given intravenously, symptomatic measures are necessary in case of an overdose, e.g.:

- Continuous control of vital signs and careful monitoring of the patient.
- Daily control of blood count to observe the need of blood transfusions, of growth factors and to detect the need of intensive care and to minimise the risk of infections.
- Measures for prevention or for therapy of paralytic ileus
- Control of circulation system and of liver function
- Broad spectrum antibiotic therapy may be necessary in case of complications due to infections. In case of a paralytic ileus, decompression by a probe may be necessary.

CONTRAINDICATIONS

Vinorelbine is contraindicated in patients with:

- Hypersensitivity to the active substance or other vinca alkaloids, or to any of the excipients.
- Neutrophil count < 1,500/mm3 or severe current or recent infection (within the last 2 weeks)
- Thrombocyte count below 100,000/mm^3
- Severe hepatic impairment not related to the tumoural process
- In combination with yellow fever vaccine.
- Pregnancy
- Lactation

STORAGE & INSTRUCTIONS:

Store in a refrigerator 2-8°C.
Protect from heat, sunlight and moisture. Do not freeze.
Keep out of the reach of children.
Single use vial. Discard unused portion.
For Intravenous Infusion use after dilution.
CONTAINS NO ANTIMICROBIAL PRESERVATIVES.

CAUTION: IT IS DANGEROUS TO TAKE THIS MEDICATION EXCEPT UNDER STRICT MEDICAL SUPERVISION.

WARNING: To be sold on the prescription of a registered oncologist or on demand from cancer hospitals and institutions only.

HOW SUPPLIED

1 Vial.

خوراک وہدایت:

سرطان کے ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو ۸-۲ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔

دھوپ، گرمی، نمی اور منجمد ہونے سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔ صرف ایک بار استعمال کے لیے ہے۔ صرف وریدی استعمال کے لیے ہے۔

انتباہ: صرف مستند اونکولوجسٹ یا کینسر ہسپتال کے نسخے پر فروخت کریں۔

Manufactured by:

PHARMASOL
PRIVATE LIMITED
Plot # 549,Sundar Industrial Estate,
Lahore, Pakistan.