

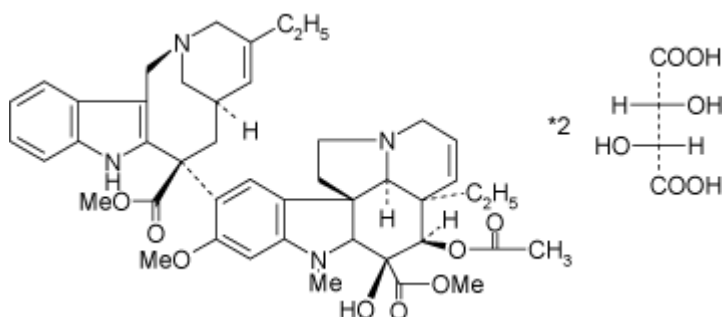
DATA SHEET

VINORELBINE EBEWE

10 mg in 1 mL and 50 mg in 5 mL Injection Concentrate

NAME OF THE MEDICINE

Vinorelbine



Chemical name: 3',4'-didehydro-4'- deoxy-C'- norvincalaukoblastine [R-(R*,R*)-2,3 dihydroxybutanedioate (1:2)(salt)]

Molecular formula: C₄₅H₅₄N₄O₈. 2C₄H₆O₆

Molecular weight: 1,079.12.

CAS: 125317-39-7 vinorelbine tartrate, 71486-22-1 vinorelbine

DESCRIPTION

Active: Vinorelbine tartrate (13.85 mg, equivalent to 10 mg vinorelbine per mL)

Inactive: Water for injection, Nitrogen

Vinorelbine Ebewe injection concentrate is a clear colourless to pale yellow solution. The aqueous solubility is > 1,000 mg/mL in distilled water. The pH of Vinorelbine Ebewe injection concentrate is approximately 3.5.

PHARMACOLOGY

Vinorelbine is a cytostatic antineoplastic medicine. It is a semisynthetic member of the vinca alkaloid family that interferes with microtubule assembly. The vinca alkaloids are structurally similar compounds comprised of two multiringed units, vindoline and catharanthine. Unlike other vinca alkaloids, the catharanthine unit is the site of structural modification for vinorelbine. The antitumour activity of vinorelbine is thought to be due primarily to inhibition of mitosis at metaphase through its interaction with tubulin. In intact tectal plates from mouse embryos, vinorelbine, vincristine, and vinblastine inhibited mitotic microtubule formation at the same concentration (2 micromolar), including a blockade of cells at metaphase. Vincristine produced depolymerisation of axonal tubules at 5 micromolar, but vinblastine and vinorelbine did not have this effect until concentrations of 30 and 40 micromolar, respectively. These data suggest relative selectivity of vinorelbine for mitotic microtubules.

Vinorelbine has an active metabolite, 17-deacetylvinorelbine, low levels of which are recovered in humans. Its toxicity and activity are slightly higher than those of vinorelbine.

Pharmacokinetics

Following intravenous administration of vinorelbine to patients at 30 mg/m², vinorelbine concentration in plasma decays in a triphasic manner. The initial rapid decline primarily represents distribution of medicine to peripheral compartments followed by metabolism and excretion of the medicine during subsequent phases. The prolonged terminal phase is due to relatively slow efflux of vinorelbine from peripheral compartments. The terminal phase half-life averages 27.7 to 43.6 hours and the mean clearance ranges from 0.6 to 1.3 L/hour/kg.

Vinorelbine demonstrated high binding to human platelets and lymphocytes. The binding to plasma constituents in cancer patients ranged from 79.6 to 92.2%. Vinorelbine binding was not altered in the presence of cisplatin, fluorouracil or doxorubicin.

Penetration of vinorelbine into pulmonary tissue is significant with tissue/plasma concentration ratios of greater than 300 in a study involving surgical biopsy.

Vinorelbine undergoes substantial hepatic elimination in humans, with large amounts recovered in faeces after intravenous administration to humans. One active metabolite, deacetylvinorelbine, has been detected but not quantified in human plasma. The effects of renal or hepatic dysfunction on the disposition of vinorelbine have not been assessed, but based on experience with other anticancer vinca alkaloids, dose adjustments are recommended for patients with impaired hepatic function (see DOSAGE AND ADMINISTRATION).

Clinical trials

Advanced breast cancer – Second Line

Twenty phase II studies of IV vinorelbine monotherapy have been performed as second-line or subsequent treatment of advanced breast cancer patients. The response rate and duration of response to chemotherapy declines as patients progress through first-, second- and third-line chemotherapy. Thirteen of these phase II studies were in mixed anthracycline-pretreated and anthracycline-naïve populations, entering 494 patients and reporting overall response rates of 14 to 45% (patients weighted average = 29.2%) and median survival times of 58 to 69 weeks. The remaining seven phase II studies were in anthracycline-pretreated patients, entering a total of 339 patients, reporting response rates of 16 to 64 % (patient weighted average = 30.9%) and median survival was 24 to 82 weeks.

The demonstration of vinorelbine activity as a single agent in the treatment of advanced breast cancer is based on eight phase II studies and one phase III study, totalling 577 patients. In the four trials where vinorelbine was used as first line treatment, the overall response rate ranged from 41 to 60%. Of the total 283 evaluable patients, 128 had objective responses (i.e. response rate of 45.2%, 95% confidence interval 39.4 to 51%, duration of response 8.7 months). In the three phase II studies of vinorelbine administered weekly in second or third line treatment of advanced breast cancer, the response rate ranged from 19.6 to 30.3%. Based on an intention-to-treat analysis of evaluable patients in the two studies which used the recommended dose of 30 mg/m² weekly, the overall response rate was 24% and median duration 4.4 months. Results of the eighth phase II study are not presented here because of the different mode of administration used.

In a randomised phase III study conducted to investigate efficacy in anthracycline refractory advanced breast cancer, 115 patients received vinorelbine as a single agent versus 64 patients who received intravenous melphalan. The median dose, number of doses and duration of treatment for vinorelbine were 27.5 mg/m², nine doses and 12 weeks, respectively and for melphalan, 25 mg/m², two doses and 8 weeks respectively. Of those receiving vinorelbine, 13 of 84 (15.5%) patients with measurable disease achieved an objective response compared with 4 of 46 (8.7%) receiving melphalan. Overall survival was 35 weeks for patients receiving vinorelbine compared with 31 weeks for those receiving melphalan (log rank p = 0.023). Neither treatment had an adverse effect on quality of life.

Vinorelbine has also been studied in combination with other agents in the second line treatment of advanced breast cancer. Results from trials are summarised in the following table (see

Table 1):

Table 1: Summary of Clinical Trials – Advanced Breast Cancer – Second Line

Agent	Number of Trials	Total No. of Patients	Overall Response Rate
Mitoxantrone	2	60	50%
5-Fluorouracil	5	221	26 – 66%
Mitomycin C	11	485	32 – 57%
Carboplatin	1	41	41%
Cisplatin	1	53	49%
Ifosfamide	2	62	28 – 36%
Paclitaxel	3	81	32 – 61%
Docetaxel	3	109	37 – 59%
Capecitabine	1	25	52%
Gemcitabine	8	301	22 – 54%
Liposomal Doxorubicin	1	33	36%

Vinorelbine was also investigated in combination with other chemotherapy agents in advanced breast cancer. In a phase II study, a combination of vinorelbine plus doxorubicin resulted in an overall response rate of 74% (66 objective responses out of 89 evaluable patients), with an overall median duration of response of 12 months and a median time to progression of 13.2 months. The median survival of patients attaining complete response had not yet been reached with a median follow up of 30 months. The median survival of patients attaining a partial response was 22.4 months. The overall median survival was 27.5 months.

In a phase II study of the combination of vinorelbine plus fluorouracil, an overall response rate of 64% was found (40 out of 63 evaluable patients), with an overall median duration of response of 12.3 months, median time to progression of 12.7 months and an overall median survival of 23 months (28.1 months for responding patients).

Non-small cell lung cancer (NSCLC)

The activity of vinorelbine was investigated in a series of phase II trials. The overall response rate to vinorelbine single agent in NSCLC patients ranged from 8 to 33% in previously untreated patients. In the two major phase II trials with more than 60 evaluable patients, the overall response rate was over 30% in chemotherapy naive patients. The high activity of vinorelbine as single agent in non-small cell lung cancer which was observed in noncontrolled phase II studies has also been confirmed in three randomised phase III trials. In one prospective randomised study with 216 stage IV patients, vinorelbine was compared to fluorouracil with calcium folinate (considered

equivalent to best supportive care for the purposes of the study). The median survival time of patients who received vinorelbine was 30 weeks compared to 22 weeks for those on the fluorouracil/calcium folinate arm (log rank $p = 0.03$). The response rates were 12% for the vinorelbine arm and 3% for the fluorouracil/calcium folinate arm.

The activity of vinorelbine in combination with cisplatin has been investigated in two randomised phase III trials in a total of 782 patients. In a two arm trial, vinorelbine was compared to vinorelbine with cisplatin. The overall response rate to vinorelbine as single agent was 16% while that of the combination vinorelbine/cisplatin was 43%. The median survival time for patients receiving vinorelbine as single agent was similar to that observed with vinorelbine and cisplatin.

In a large European clinical trial, 612 patients with stage III or IV non-small cell lung cancer, no prior chemotherapy and WHO performance status of 0, 1 or 2 were randomised to treatment with single-agent vinorelbine (30 mg/m²/week), vinorelbine (30 mg/m²/week) plus cisplatin (120 mg/m² days 1 and 29 then every six weeks), and vindesine (3 mg/m²/week for seven weeks, then every second week) plus cisplatin (120 mg/m² days 1 and 29 then every six weeks). Vinorelbine plus cisplatin produced longer survival times than vindesine plus cisplatin (median survival 40 weeks versus 32 weeks, $p = 0.03$). The median survival time for patients receiving single agent vinorelbine was similar to that observed with vindesine plus cisplatin (31 weeks versus 32 weeks). The one year survival rates were 36% for vinorelbine plus cisplatin, 27% for vindesine plus cisplatin, and 30% for single agent vinorelbine. The overall objective response rate (all partial responses) was significantly higher in patients treated with vinorelbine plus cisplatin (28%) than in those treated with vindesine plus cisplatin (19%, $p = 0.03$) and in those treated with single-agent vinorelbine (14%, $p < 0.001$). The response rates reported for vindesine plus cisplatin and single agent vinorelbine were not significantly different. Significantly, less nausea, vomiting, alopecia, and neurotoxicity were observed in patients receiving single-agent vinorelbine compared to those receiving the combination of vindesine and cisplatin.

INDICATIONS

Treatment of advanced breast cancer after failure of standard therapy, as a single agent or in combination; and as first-line treatment for advanced non-small cell lung cancer, as a single agent or in combination.

CONTRAINDICATIONS

Known hypersensitivity to vinorelbine or other vinca alkaloids
Neutrophil counts $< 1,000$ cells/mm³ or severe infection due to neutropenia.
Platelet count $< 100,000$ /mm³
Severe hepatic insufficiency.
Pregnancy (see Use in Pregnancy).
Lactation (see Use in Lactation).
In combination with yellow fever vaccine (see PRECAUTIONS).

PRECAUTIONS

Vinorelbine injection should be administered under the supervision of a doctor experienced in the use of cancer chemotherapeutic agents.

Administration

Vinorelbine Ebewe must only be administered by the intravenous route. Intrathecal administration of other vinca alkaloids has resulted in death. Improper administration of Vinorelbine Ebewe may result in extravasation causing local tissue necrosis and/or thrombophlebitis (see DOSAGE AND ADMINISTRATION, Administration precautions).

Myelosuppression

Since inhibition of the haematopoietic system is the main risk association with vinorelbine, patients treated with vinorelbine should be frequently monitored for myelosuppression both during and after therapy, with determination of haemoglobin level and the leukocyte, neutrophil and platelet counts on the day of each new administration. Neutropenia is dose-limiting. Neutrophil nadirs occur between five and ten days after dosing, depending on whether vinorelbine is used as single agent or in combination, with neutrophil count recovery usually within 7 to 14 days after administration. Complete blood counts with differentials should be performed and results reviewed prior to administering each dose of Vinorelbine Ebewe. Vinorelbine Ebewe should not be administered to patients with neutrophil counts $< 1,000$ cells/mm³. Patients developing severe neutropenia should be monitored carefully for evidence of infection and/or fever. If patients present signs or symptoms suggestive of infection, a prompt investigation should be carried out (see DOSAGE AND ADMINISTRATION for recommended dose adjustments for neutropenia).

Vinorelbine Ebewe should be used with extreme caution in patients whose bone marrow reserve may have been compromised by prior irradiation or chemotherapy, or whose marrow function is recovering from the effects of previous chemotherapy (see DOSAGE AND ADMINISTRATION).

Laboratory tests

Since dose-limiting clinical toxicity is the result of depression of the white blood cell count, it is imperative that complete blood counts with differentials be obtained and reviewed on the day of treatment prior to each dose of Vinorelbine Ebewe.

General

Most medicine-related adverse events of vinorelbine are reversible. If severe adverse events occur, Vinorelbine Ebewe should be reduced in dosage or discontinued and appropriate corrective measures taken. Reinstitution of therapy with vinorelbine should be carried out with caution and alertness as to possible recurrence of toxicity.

Patients presenting with ischaemic cardiac disease should be carefully monitored (see ADVERSE EFFECTS).

Acute shortness of breath and severe bronchospasm have been reported infrequently following the administration of vinorelbine and other vinca alkaloids, most commonly when the vinca alkaloid was used in combination with mitomycin. These adverse events may require treatment with supplemental oxygen, bronchodilators, and/or corticosteroids, particularly when there is a pre-existing pulmonary dysfunction.

Care must be taken to avoid contamination of the eye with concentrations of Vinorelbine Ebewe used clinically. Severe irritation of the eye has been reported with accidental exposure to another vinca alkaloid, and even corneal ulceration if the medicine is sprayed under pressure. If exposure occurs, the eye should immediately be thoroughly flushed with water or sodium chloride 9 mg/mL (0.9%) solution for injection.

Vinorelbine Ebewe should not be given concomitantly with radiotherapy if the treatment field includes the liver.

This product is specifically contraindicated with yellow fever vaccine and its concomitant use with other live attenuated vaccines is not recommended.

Caution must be exercised when combining vinorelbine and strong inhibitors or inducers of CYP3A4 (see INTERACTIONS WITH OTHER MEDICINES. Interactions specific to vinorelbine), and its combination with phenytoin (like all cytotoxics) and with itraconazole (like all vinca-alkaloids) is not recommended.

Impaired renal function

Because of the low level of renal excretion, no dose modification is necessary in patients with renal impairment (see DOSAGE AND ADMINISTRATION).

Impaired hepatic function

There is no evidence that the toxicity of vinorelbine is enhanced in patients with elevated liver enzymes. No data are available for patients with severe baseline cholestasis, but the liver plays an important role in the metabolism of vinorelbine. Because clinical experience in patients with severe liver disease is limited, caution should be exercised when administering Vinorelbine Ebewe to patients with severe hepatic injury or impairment.

Use in the elderly

Clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenicity/mutagenicity

Vinorelbine tartrate 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 or cytotoxic in a reverse histidine mutation (Ames) test but showed mutagenic potential in a mouse forward mutation (TK locus) test. Carcinogenicity studies in mice and rats showed no tumorigenic activity at dose levels up to 2.4 mg/m² given by intravenous injection every two weeks for 18 months or two years, respectively.

However, the positive findings in genetic toxicity assays suggest that the medicine may have carcinogenic potential at the higher dose level used in humans.

Effects on fertility

Adverse effects on the male reproductive system were observed in repeat-dose toxicity studies in animals, including decreased spermatogenesis in rats dosed twice weekly at 2.1 to 7.2 mg/m² for 13 weeks, reduced prostate/seminal vesicle secretion in rats dosed twice weekly at 3 mg/m² for 26 weeks, reduced testicular weight in mice dosed at 19 mg/m²/day for three 5-day cycles, and reduced epididymal weight in dogs dosed at 5 mg/m² for 26 weeks. Vinorelbine tartrate did not affect fertility when administered to male and female rats prior to and during mating; however, the doses used in these studies (9 mg/m² once weekly or up to 4.2 mg/m² at three-day intervals) were lower than the human dose.

Men being treated with vinorelbine are advised not to father a child during and minimally up to 3 months after treatment. Prior to treatment, advice should be sought for conserving sperm due to the chance of irreversible infertility as a consequence of treatment with vinorelbine.

Use in pregnancy (Category D)

Medicines which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These medicines may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Vinorelbine may cause foetal harm if administered to a pregnant woman. Vinorelbine is contraindicated in pregnancy (see CONTRAINDICATIONS).

When given every three days during organogenesis, vinorelbine tartrate has been shown to be teratogenic in rats and rabbits at doses of 3 and 7.7 mg/m², respectively. A single 9 mg/m² dose of vinorelbine tartrate caused embryogenic deaths in mice. Doses causing adverse foetal effects in animals were lower than the human dose. There are no studies in pregnant women. If Vinorelbine Ebewe is used during pregnancy, or if the patient becomes pregnant while receiving this medicine, the patient should be apprised of the potential hazard to the foetus. Women of child-bearing potential should be advised to avoid becoming pregnant during therapy with Vinorelbine Ebewe. Women of child-bearing potential must use effective contraception during treatment and up to 3 months after treatment. **Use in lactation.** It is not known whether vinorelbine is excreted in the milk of animals or humans. A study in rats showed that growth of the offspring was suppressed when vinorelbine tartrate was administered to lactating dams at 6 mg/m² every three days. Because many medicines are excreted in human milk, and because of the potential for serious

adverse effects in breastfeeding infants from vinorelbine, it is recommended that breastfeeding be discontinued in women who are receiving therapy with Vinorelbine Ebewe.

Paediatric use

Safety and effectiveness have not been established.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed but on the basis of the pharmacodynamic profile vinorelbine does not affect the ability to drive and use machines. However, caution is necessary in patient treated with vinorelbine considering some adverse effects of the medicine.

INTERACTIONS WITH OTHER MEDICINES

Interactions specific to vinorelbine

The combination of vinorelbine with other medicines with known bone marrow toxicity is likely to exacerbate the myelosuppressive adverse effects.

Acute pulmonary effects have been reported with vinorelbine and other vinca alkaloids used in conjunction with mitomycin. The risk of bronchospasm and dyspnoea is increased, in rare case interstitial pneumonitis was observed. Vinorelbine Ebewe should be administered with caution in combination with mitomycin. Although the pharmacokinetics of vinorelbine are not influenced by the concurrent administration of cisplatin, the incidence of toxicities, specifically granulocytopenia, with the combination of vinorelbine and cisplatin is significantly higher than with single-agent vinorelbine.

In studies with rats, the anticoagulant effect of phenindione was potentiated when given in combination with high doses of vinorelbine (30 mg/ m²/day for four consecutive days or 15 mg/ m²/day for five consecutive days) but combination treatment with sodium valproate did not cause any increase in anticonvulsant activity.

Based on the available limited information, it is possible that interaction may occur with other medicines which are metabolised via the cytochrome CYP3A4. As CYP3A4 is mainly involved in the metabolism of vinorelbine, combination with strong inhibitors of this isoenzyme (e.g. ketoconazole, itraconazole) could increase blood concentrations of vinorelbine and combination with strong inducers of this isoenzyme (e.g. rifampicin, phenytoin) could decrease blood concentrations of vinorelbine.

Interactions common to all cytotoxics

Due to the increase of thrombotic risk in case of tumoral diseases, the use of anticoagulative treatment is frequent. The high intra-individual variability of the coagulability during diseases, and the eventuality of interaction between oral anticoagulants and anticancer chemotherapy required, if it is decided to treat the patient with oral anticoagulants, to increase frequency of the INR (International Normalised Ratio) monitoring.

Concomitant use contraindicated

Yellow fever vaccine: risk of fatal generalised vaccine disease (see CONTRAINDICATIONS).

Concomitant use not recommended

Live attenuated vaccines (for yellow fever vaccine see CONTRAINDICATIONS): risk of generalised vaccine disease, possibly fatal. This risk is increased in patients already immunodepressed by their underlying disease. It is recommended to use an inactivated when exists (poliomyelitis).

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

Concomitant use to take into consideration

Cyclosporine, tacrolimus: excessive immunodepression with risk of lymphoproliferation

Interactions specific to vinca-alkaloids

Concomitant use not recommended

Itraconazole: increased neurotoxicity of vinca-alkaloids due to the decrease of their hepatic metabolism.

Concomitant use to take into consideration

Mitomycin: risk of bronchospasm and dyspnoea is increased, in rare case interstitial pneumonitis was observed.

Acute pulmonary effects have been reported with vinorelbine and other vinca alkaloids used in conjunction with mitomycin. Vinorelbine Ebewe should be administered with caution in combination with mitomycin.

As vinca-alkaloids are known as substrates for P-glycoprotein, and in the absence of specific study, caution should be exercised when combining Vinorelbine with strong modulators of this membrane transporter.

ADVERSE EFFECTS

Adverse effects reported as more than isolated cases are listed below, by system organ class and by frequency. *Frequencies are defined as: very common (> 1/10), common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100), rare (> 1/10,000, < 1/1,000), very rare (< 1/10,000),* according to the MedDRA frequency convention and system organ classification.

Additional adverse effects from post-marketing experience have been added according to the MedDRA classification.

Some effects were previously described using the WHO classification (grade 1=G1 ; grade 2=G2 ; grade 3=G3 ; grade 4=G4 ; grade 1-4=G1-4 ; grade 1-2=G1-2 ; grade 3-4=G3-4).

The most commonly reported adverse medicine effects are bone marrow depression with neutropenia, anaemia, neurologic disorders, gastrointestinal toxicity with nausea, vomiting, stomatitis and constipation, transient elevations of liver function tests, alopecia and local phlebitis.

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:

Complicated septicemia and sometimes fatal

Not known:

Neutropenic sepsis

Blood and lymphatic system disorders

Very common:

Haematological. Neutropenia is the major dose-limiting toxicity with vinorelbine. Neutropenia (G 3: 25.2%, G 4: 28.4%) is rapidly reversible (7 to 14 days) and noncumulative. It is maximal between five and fourteen days after administration, depending on whether vinorelbine is used as

single agent or in combination. Further treatment may be given after recovery of the neutrophil count. Anaemia (G 3 to 4: 8%)

Common:

Thrombocytopenia (G 3-4: 2.3%) can also occur. Dose adjustments are required for haematological toxicity and hepatic insufficiency (see DOSAGE AND ADMINISTRATION).

Not known:

Febrile neutropenia

Immune system disorders

Not known:

Systemic allergic reactions as anaphylaxis, anaphylactic shock or anaphylactoid type reaction

Endocrine disorders

Uncommon:

Inappropriate antidiuretic hormone secretion (SIADH)

Metabolism and nutrition disorders

Rare:

Severe hyponatraemia

Not known:

Anorexia

Nervous system disorders

Very common:

Mild to moderate peripheral neuropathy manifested by paraesthesia and loss of deep tendon reflexes (G 3: 2.5%, G 4: 0.2%) and hyperaesthesia has been reported. After prolonged treatment weakness of the lower extremities has also been reported. The effects are dose dependent but usually reversible when treatment is discontinued.

In autonomic neuropathy, the main symptom is intestinal paresis causing constipation which rarely progresses to paralytic ileus (G 3: 2%, G 4: 0.6%). Treatment may be resumed after recovery of normal bowel mobility.

Uncommon:

Severe paraesthesias with sensory and motor symptoms are infrequent. These effects are generally reversible.

Gastrointestinal disorders

Very common:

Constipation (see Nervous system disorders, above), mild to moderate nausea occurred in 25.5% of patients treated with vinorelbine.

Stomatitis (as single agent)

Nausea and vomiting (G 3: 2%, G 4: 0.3%) Anti-emetic therapy may reduce their occurrence. Constipation is the main symptom which rarely progresses to paralytic ileus with vinorelbine as single agent and with the combination of vinorelbine and other chemotherapeutic agents.

Common:

Diarrhoea, usually mild to moderate, may occur.

Rare:

Paralytic ileus, treatment may be resumed after recovery of normal bowel mobility.

Pancreatitis has been reported very rarely.

Skin and subcutaneous tissue disorders

Very common:

Alopecia is mild and may appear progressively with extended courses of treatment.

Vinorelbine may produce generalised cutaneous effects.

Like other anticancer vinca alkaloids, vinorelbine is a moderate vesicant.

Injection site effects, including erythema, pain at injection site, and vein discolouration occurred in approximately one-third of patients (5% were severe). Chemical phlebitis along the vein proximal to the site of injection was reported in 10% of patients. In rare cases local tissue necrosis has been observed. Bolus injection followed by liberal flushing of the vein can limit this effect. Insertion of a central venous line may be necessary.

Not known:

Erythema on hands and feet

Hepatobiliary disorders

Very common:

Transient elevations of liver enzymes were reported without clinical symptoms.

Musculoskeletal and connective tissue disorders

Common:

Arthralgia including jaw pain and myalgia

Respiratory system, thoracic and mediastinal disorders

Common:

Shortness of breath was reported in 3% of patients.

Uncommon:

Vinorelbine, like other vinca alkaloids, may produce dyspnoea and bronchospasm.

Rare:

Interstitial pneumopathy has been reported, in particular in patients treated with vinorelbine in combination with mitomycin.

Cardiac disorders

Common:

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 tumour within the chest.

Rare:

A few cases of myocardial infarction angina pectoris and/or transient ECG changes have been reported (see PRECAUTIONS).

Very rare:

Tachycardia, palpitation and heart rhythm disorders

In very rare cases, cardiac failure and pulmonary oedema have been reported during treatment with vinorelbine, however a causal relationship has not been established.

Vascular disorders

Uncommon:

Hypotension, hypertension, flushing and peripheral coldness

Rare:

Severe hypotension, collapse

General disorders and administration site conditions

Very common:

Effects at the injection site may include erythema, burning pain, vein discoloration and local phlebitis with vinorelbine as single chemotherapeutic agent.

Common:

Asthenia, fatigue, fever, pain at different locations including chest pain and pain at the tumour site have been experienced by patients receiving vinorelbine therapy.

Rare:

Local necrosis has been observed. Proper positioning of the intravenous needle or catheter and bolus injection followed by liberal flushing of the vein can limit these effects.

Other

Fatigue occurred in 27% of patients. It was usually mild or moderate but tended to increase with cumulative dosing. Other reported toxicities occurring in less than 5% of patients include jaw pain, myalgia, arthralgia, pain at the tumour site, and rash. Chest pain of non-cardiac origin has also been reported. Haemorrhagic cystitis and the syndrome of inappropriate ADH secretion were each reported in < 1% of patients. Rare cases of severe hyponatraemia have been reported (see Table 2).

Table 2: Advanced Events Observed in Pivotal Phase III Studies

Adverse event	Total Vinorelbine % (n=1,833)*	Total Vinorelbine combined** % (n=641)*	VDS + CDDP % (n=192)*	FU + CF % (n=68)*
Haematological				
Neutropenia				
Grade 4	28.4	46.2	22.0	15.2
Grade 3	25.2	18.1	25.7	9.1
All grades	78.2	83.7	79.1	47.0
Anaemia				
Grade 4	1.1	1.6	-	0.0
Grade 3	6.9	9.0	-	1.5
All grades	70.0	71.5	-	43.9
Leucopenia				
Grade 4	8.9	14.8	3.1	3.0
Grade 3	30.1	29.2	23.6	13.6
All grades	82.2	83.9	80.1	40.8
Thrombocytopenia				
Grade 4	1.1	0.9	0.5	1.5
Grade 3	1.2	1.1	2.6	0.0
All grades	7.4	10.1	9.9	3.0

Neurological				
Peripheral neuropathy				
Grade 4	0.2	0.4	1.0	0.0
Grade 3	2.5	4.5	16.1	0.0
All grades	24.6	30.0	58.2	1.5
Gastrointestinal				
Constipation				
Grade 4	0.6	1.2	-	0.0
Grade 3	2.0	2.9	-	1.5
All grades	25.5	26.9	-	5.9
Nausea/vomiting				
Grade 4	0.3	1.4	1.0	2.9
Grade 3	2.0	18.4	24.0	0.0
All grades	31.3	68.1	72.4	24.9
Dermatological				
Alopecia				
Grade 4	0.1	0.4	0.0	0.0
Grade 3	3.7	19.7	13.5	2.9
All grades	23.9	57.2	56.2	10.3
Local phlebitis				
Grade 4	0.1	0.5	0.0	0.0
Grade 3	3.3	3.2	0.0	0.0
All grades	22.5	19.8	6.8	1.5
Cardiovascular				
Cardiac events				
Grade 4	0.3	2.3	-	0.0
Grade 3	0.6	0.5	-	0.0
All grades	3.0	5.1	-	3.0
Others				
Infection				
Grade 4	1.2	7.1	-	0.0
Grade 3	1.5	5.3	-	0.0
All grades	12.0	26.8	-	0.0

* Maximum number of evaluable patients

** Combined medicines: cisplatin, cisplatin and etoposide, fluorouracil, mitomycin, vindesine, ifosfamide, actinomycin, epirubicin, doxorubicin

VDS = vindesine

CDDP = cisplatin

FU = fluorouracil

CF = calcium folinate

DOSAGE AND ADMINISTRATION

Vinorelbine Ebewe contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

Adults

Single-agent treatment is usually given at 25 to 30 mg/m² weekly.

In combination chemotherapy the dose may be the same and the frequency of administration reduced, i.e. days 1 and 8 or days 1 and 5 every three weeks.

Vinorelbine Ebewe should be administered either by slow bolus over six to ten minutes after dilution in 50 mL of a normal saline solution or by a short infusion over 20 to 30 minutes after dilution in 125 mL of normal saline solution. Administration should always be followed by at least 250 mL normal saline infusion to flush the vein.

Dosage modifications for haematological toxicity

Neutrophil counts should be greater than or equal to 1,000 cells/mm³ prior to the administration of Vinorelbine Ebewe. Adjustments in the dosage of Vinorelbine Ebewe should be based on neutrophil counts obtained on the day of treatment (see Table 3).

Table 3: Dosage Modifications for Haematological Toxicity

Neutrophils (cells/mm ³) on Day of Treatment	Dose of Vinorelbine Ebewe (mg/m ²)
≥ 1500	30
1000 to 1499	15
< 1000	Do not administer. Repeat neutrophil count in one week. If three consecutive weekly doses are withheld because neutrophil count is < 1000 cells/mm ³ , discontinue Vinorelbine Ebewe

Note. For patients who, during treatment with vinorelbine, have experienced fever and/or sepsis while neutropenic or who have had two consecutive weekly doses withheld due to neutropenia, subsequent doses of vinorelbine should be 22.5 mg/m² if the neutrophil count is greater than or equal to 1,500 cells/mm³ or 11.25 mg/m² if the neutrophil count is 1,000 to 1,499 cells/mm³.

Dosage modifications for hepatic insufficiency

Vinorelbine Ebewe should be administered with caution to patients with hepatic insufficiency. In patients who develop hyperbilirubinaemia during treatment with Vinorelbine Ebewe, the dose should be adjusted on the basis of total bilirubin, as a measure of hepatic function (see Table 4).

Table 4: Dose Modification Based on Total Bilirubin

Total Bilirubin (mg/dL)	Dose of Vinorelbine Ebewe (mg/m ²)
≤ 2.0	30
2.1 to 3.0	15
> 3.0	7.5

For patients with both haematological toxicity and hepatic insufficiency, the lower of the doses listed above should be administered.

Administration precautions

Caution. Vinorelbine Ebewe must only be administered intravenously through an infusion line. It is extremely important that the intravenous needle or catheter be properly positioned before any vinorelbine is injected. Leakage into surrounding tissue during intravenous administration of Vinorelbine Ebewe may cause considerable irritation, local tissue necrosis and/or thrombophlebitis. If extravasation occurs, the injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein. Since there are no established guidelines for the treatment of extravasation injuries with vinorelbine, institutional guidelines may be used. As with other toxic compounds, caution should be exercised in handling and preparation of the solution of Vinorelbine Ebewe. Skin effects may occur with accidental exposure. The use of gloves is recommended. If the solution of Vinorelbine Ebewe contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water. Severe irritation of the eyes has been reported with accidental contamination of the eye with another vinca alkaloid. If this happens with Vinorelbine Ebewe, the eye should be flushed with water immediately and thoroughly.

Procedures for proper handling and disposal of anticancer medicines should be used. Several guidelines on this subject have been published.

Vinorelbine Ebewe injection is a clear, colourless to pale yellow solution. Parenteral medicine products should be visually inspected for particulate matter and discolouration prior to administration whenever solution and container permit. If particulate matter is seen, Vinorelbine Ebewe should not be administered.

Preparation for administration. Vinorelbine Ebewe injection must be diluted in either a syringe or intravenous bag using one of the recommended solutions. The volume of dilution depends on the mode of administration: 50 mL for a bolus injection; 125 mL for an infusion.

Administration of Vinorelbine Ebewe must be followed by infusion of at least 250 mL of one of the recommended solutions.

Diluted Vinorelbine Ebewe is chemically and physically stable for up to 24 hours under normal room light below 30°C when stored in polypropylene syringes, polyvinyl chloride bags and clear glass vials. However, to reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2°C to 8°C for not more than 24 hours.

Syringe. The calculated dose of Vinorelbine Ebewe should be diluted to a concentration between 1.5 and 3.0 mg/mL. The following solutions may be used for dilution: Glucose 5% Injection USP and Sodium Chloride 0.9% Injection USP.

Intravenous bag. The calculated dose of Vinorelbine Ebewe should be diluted to a concentration between 0.5 and 2 mg/mL. The following solutions may be used for dilution: Glucose 5% Injection USP; Sodium Chloride 0.9% Injection USP; Sodium Chloride 0.45% Injection USP; Glucose 5% and Sodium Chloride 0.45% Injection USP; Ringer's Injection USP and Lactated Ringer's Injection (Compound Sodium Lactate Injection) USP.

After diluting Vinorelbine Ebewe in normal saline or glucose solution, the shelf-life in the clear glass vials or in PVC perfusion bags is 24 hours at storage below 30°C.

Vinorelbine Ebewe should not be diluted in alkaline solutions due to the risk of precipitation. Vinorelbine Ebewe should not be mixed with other agents. Vinorelbine Ebewe is not absorbed to or affected by either PVC or clear neutral glass.

To reduce microbiological hazard, use as soon as practicable after preparation. If storage is necessary, hold at 2 to 8°C for not more than 24 hours.

As with all parenteral medicine products, intravenous admixtures should be inspected visually for clarity, particulate matter, discolouration and leakage prior to administration, whenever solution and container permit.

OVERDOSAGE

Contact the Poisons Information Centre on (telephone Australia 13 11 26 or New Zealand 0800 POISON or 0800 764766) for advice on management of overdose.

Symptoms

Overdosage with vinorelbine could produce bone marrow hypoplasia sometimes associated with infection, fever and paralytic ileus.

Emergency procedure

General supportive measures together with blood transfusion, growth factors and broad spectrum antibiotic therapy should be instituted as deemed necessary by the physician.

There is no known antidote for overdoses of vinorelbine. The primary anticipated complications of overdosage would consist of bone marrow suppression and peripheral neurotoxicity. If overdosage occurs, general supportive measures together with appropriate blood transfusions and antibiotics should be instituted as deemed necessary by the doctor.

PRESENTATION AND STORAGE CONDITIONS

Injection vial (clear, colourless to pale yellow solution; single use vial)

Each injection vial contains 13.85 mg vinorelbine tartrate, equivalent to 10 mg vinorelbine per mL

10mg in 1mL vial: 1's and 5's

50mg in 5mL vial: 1's

Store at 2°C to 8°C. (Refrigerate. Do not freeze). Protect from light.

MEDICINE CLASSIFICATION

Prescription Medicine

NAME AND ADDRESS OF SPONSOR

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Mt Wellington
Auckland

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