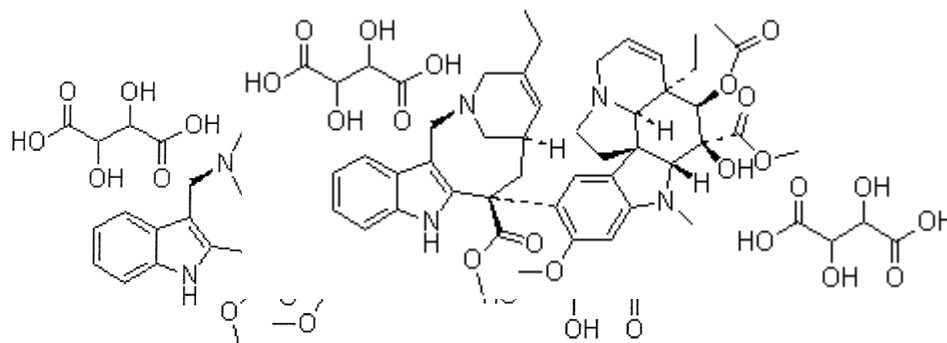


PRODUCT INFORMATION

VINORELBINE 10 LINK (Vinorelbine 10 mg/1mL Concentrated Injection) VINORELBINE 50 LINK (Vinorelbine 50 mg/5mL Concentrated Injection)

NAME OF MEDICINE

The name of the medicine is vinorelbine as vinorelbine tartrate (vinorelbine bitartrate).



Chemical name: 3',4'-didehydro-4'-deoxy-C'-norvincalcoloblastine (R-(R*,R*)-2,3 dihydroxybutanedioate (1:2)(salt)).

Molecular Formula: C₄₅H₅₄N₄O₈·2(C₄H₆O₆) **Molecular Weight:** 1079.12

CAS Registry Number: 125317-39-7

DESCRIPTION

Vinorelbine tartrate is a semi-synthetic vinca alkaloid with anti-tumour activity. It is a concentrated solution administered after dilution via intravenous infusion. It is a clear, white to yellow or light brown amorphous powder. Dissolved in water vinorelbine is a clear, colourless to pale yellow solution.

Each vial contains vinorelbine tartrate equivalent to 10 mg (1mL vial) or 50 mg (5mL vial) vinorelbine in Water for Injections. VINORELBINE LINK contains no preservatives or other additives are present. The aqueous solution is sterile and nonpyrogenic.

The aqueous solubility is > 1000 mg/mL in distilled water. The pH of VINORELBINE LINK injection is approximately 3.5.

PHARMACOLOGY

Vinorelbine is a cytostatic antineoplastic drug. It is a semi-synthetic 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 antitumor 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 ($2\mu\text{M}$), including a blockade of cells at metaphase. Vincristine produced depolymerisation of axonal tubules at $5\mu\text{M}$, but vinblastine and vinorelbine did not have this effect until concentrations of $30\mu\text{M}$ and $40\mu\text{M}$, 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/m^2 , 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. The terminal phase half-life averages 27.7 to 43.6 hours and the mean clearance ranges from 0.6 to 1.3 L/h/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. 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 the patient 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 14-45% (patients weighted average = 29.2%) and median survival times of 58-69 weeks.

The remaining seven phase II studies were in anthracycline-pretreated patients, entering a total of 339 patients, reporting response rates of 16-64% (patients weighted average = 30.9%) and median survival was 24-82 weeks.

In a randomised phase III study conducted to investigate efficacy in anthracycline-refractory advanced breast cancer one hundred and fifteen patients received vinorelbine as a single agent versus sixty four patients who received intravenous melphalan. The median dose, number of doses and duration of treatment for vinorelbine were 27.5 mg/m², 9 doses and 12 weeks, respectively and for melphalan, 25 mg/m², 2 doses and 8 weeks, respectively. Of those receiving vinorelbine, thirteen of 84 (15.5%) patients with measurable disease achieved an objective response compared with four 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 of treatment of advanced breast cancer. Results from trials are summarised in the following table.

Agent	No. of Trials	Total No. of Patients	Overall Response rate
Mitoxantrone	2	60	50%
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%

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 a 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 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 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 a 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 < 1x10⁹ cells/L, or severe infection due to neutropenia.

Severe hepatic insufficiency.

Pregnancy.

Lactation.

PRECAUTIONS

VINORELBINE LINK should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.

Administration

VINORELBINE LINK must only be administered by the intravenous route. Intrathecal administration of other vinca alkaloids has resulted in death. Improper administration of VINORELBINE LINK may result in extravasation causing local tissue necrosis and/or thrombophlebitis (see ADMINISTRATIVE PRECAUTIONS).

Myelosuppression

Patients treated with VINORELBINE LINK should be frequently monitored for myelosuppression both during and after therapy. Neutropenia is dose-limiting. Neutrophil nadirs occur between 5 and

10 days after dosing, depending on whether VINOELBINE LINK 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 VINOELBINE LINK. VINOELBINE LINK should not be administered to patients with neutrophil counts $< 1 \times 10^9$ cells/L. 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.)

VINOELBINE LINK 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).

Neurological, Peripheral Neuropathy

The effects are dose dependent but usually reversible when treatment is discontinued.

Neurological, Autonomic Neuropathy

Treatment may be resumed after recovery of normal bowel motility.

General

Most drug-related adverse effects of VINOELBINE LINK are reversible. If severe adverse events occur, VINOELBINE LINK should be reduced in dosage or discontinued and appropriate corrective measures taken. Reinstitution of therapy with VINOELBINE LINK 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 VINOELBINE LINK 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 VINOELBINE LINK used clinically. Severe irritation of the eye has been reported with accidental exposure to another vinca alkaloid, and even corneal ulceration if the drug is sprayed under pressure. If exposure occurs, the eye should immediately be thoroughly flushed with water.

There is no evidence that the toxicity of VINOELBINE LINK 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 VINOELBINE LINK. Because clinical experience in patients with severe liver disease is limited, caution should be exercised with administering VINOELBINE LINK to patients with severe hepatic injury or impairment. VINOELBINE LINK should not be given concomitantly with radiotherapy if the treatment field includes the liver.

Because of the low level of renal excretion, no dose modification is necessary in patients with renal impairment.

Others

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

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 3-day intervals) were lower than the human dose.

Use in Pregnancy

Category D - Drugs that have caused or are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

VINORELBINE LINK may cause fetal harm if administered to a pregnant woman. 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 fetal effects in animals were lower than the human dose. There are no studies in pregnant women. If VINORELBINE LINK is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with VINORELBINE LINK.

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 drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from VINORELBINE LINK, it is recommended that nursing be discontinued in women who are receiving therapy with VINORELBINE LINK.

Paediatric Use

Safety and effectiveness have not been established.

Use in 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

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 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 drug may have carcinogenic potential at the higher dose level used in humans.

Genotoxicity

Vinorelbine can have genotoxic effects. Women of childbearing potential must use an effective method of contraception during treatment and three months thereafter.

Interactions with Other Medicines

Acute pulmonary reactions have been reported with vinorelbine and other vinca alkaloids used in conjunction with mitomycin. VINORELBINE LINK 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 4 consecutive days or 15 mg/m²/day for 5 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 drugs which are metabolised via the cytochrome CYP3A4.

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 LINK.

Effects on the ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed.

ADVERSE EFFECTS

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) and very rare (<1/10,000).

Haematological:

Very Common: bone marrow depression resulting mainly in neutropenia.

Common: anaemia, thrombocytopenia.

Neurological:

Common: peripheral neuropathy manifested as paraesthesia, hyperaesthesia and loss of deep tendon reflexes, autonomic neuropathy manifested as intestinal paresis and constipation, weakness of the lower extremities, autonomic neuropathy.

Rare: paralyticileus

Gastrointestinal:

Very Common: stomatitis, nausea.

Common: constipation (see Neurological), severe nausea and vomiting, diarrhoea

Rare: pancreatitis

Dermatological:

Very Common: injection site reactions including erythema, pain, vein discoloration and phlebitis

Common: severe injection site reactions, alopecia.

Rare: generalised cutaneous reactions, tissue necrosis at injection site.

Hepatic:

Very common: transient elevations of liver enzymes

Respiratory:

Common: shortness of breath, bronchospasm.

Rare: interstitial pneumopathy (in particular, with vinorelbine and mitomycin combinations).

Cardiovascular:

Common: chest pain.

Rare: myocardial infarction, angina pectoris, transient electrocardiogram changes.

Very rare: cardiac failure, pulmonary oedema.

Musculoskeletal:

Common: jaw pain, myalgia, arthralgia.

Genitourinary:

Uncommon: haemorrhagic cystitis, inappropriate antidiuretic hormone (ADH) secretion.

Metabolism and nutrition disorders

Rare: severe hyponatraemia

General:

Very Common: fatigue

Common: infection, pain at the tumour site, chest pain of non-cardiac origin.

Uncommon: severe sepsis.

Adverse Events Observed in Pivotal Phase III studies (metastatic)

	Total NAVELBINE® %	Total NAVELBINE® combined* %	VDS + CDDP %	5 FU + LV %
Maximum number of evaluable patients	N= 1833	N=641	N=192	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
-Laukopenia				
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
-Thombocytopenia				
Grade 4	1.1	0.9	0.5	1.5
Grade 3	1.2	1.1	2.6	0.0
All grade	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

	Total NAVELBINE® %	Total NAVELBINE® combined* %	VDS + CDDP %	5 FU + LV %
Maximum number of evaluable patients	N= 1833	N=641	N=192	N=68
GASTRO-INTESTINAL				
-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				

Product Information:

Vinorelbine 10 Link & Vinorelbine 50 Link (10mg/1mL and 50mg/5 mL)

Ver 3 Approved

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

*Combined drugs : cisplatin, cisplatin + etoposide, 5 FU, mitomycin, vindesine, ifosfamide, actinomycin, epirubicin, doxorubicin.

VDS= vindesine

CDDP = cisplatin

LV = Leucovorin

Adverse Events observed in the adjuvant trial with an incidence > 1 % in the treatment and control groups

Adverse events by MEDRA terms	i.v VRL + CDDP	Control Groups
Blood and Lymphatic system disorders		
Leucopenia	91.2	4.8
Neutropenia	92.0	3.5
Anemia	77.7	6.1
Thrombocytopenia	14.3	0.5
Cardiac disorder		
Cardiac failure	4.3	2.6
Pericarditis	0.3	1
Sinus tachycardia	7.2	2.6
Ventricular extrasystoles	2.3	1.8
Gastrointestinal disorder		
Constipation	44.7	4.7
Diarrhoea	15.5	2.1
Nausea	50.1	5.2
Stomatitis	13.2	2.6
Vomiting	53.9	1.3
General Disorder and administration site conditions		
Athenia	81.9	31.8
Pain	43.6	39.6
Pyrexia	31.5	7.1
Infections and infestations		
Infection	29.5	10.2
Septic shock	2.3	-
Metabolism and nutrition disorder		
Anonexia	70.8	17.3
Nervous system disorder		
Nauropathy peripheral	28.4	1.0
Respiratory, thoracic and mediastinal disorder		
Dyspnea at rest	1.7	2.9
Dyspnea exertional	8.0	10.0
Lung disorder	23.5	28.9
Skin and subcutaneous tissue disorders		
Alopecia	57.3	-
Erythema	2.6	1.3
Skin disorder	2.3	-

Vascular disorders		
Phlebitis	18.1	-

DOSAGE AND ADMINISTRATION

VINORELBINE LINK must be administered under the supervision of a doctor experienced in the use of chemotherapy. VINORELBINE LINK should not be diluted with alkaline solutions (risk for precipitation). Product is for single use in one patient only. Discard any residue.

Strictly by intravenous injection through an infusion line.

The use of intrathecal route is contra-indicated.

In adults:

- Vinorelbine is usually given at 25-30 mg/m² weekly.

VINORELBINE LINK may be administered by slow bolus (6-10 minutes) after dilution in 20 – 50 ml of normal saline or glucose 50 mg/ml (5%) solution or by a short infusion (20-30 minutes) after dilution in 125 ml of normal saline or glucose 50 mg/ml (5%) solution. Administration should always be followed by at least 250 mL normal saline infusion to flush the vein.

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.

Hepatic Impairment

In breast cancer-patients, vinorelbine clearance is not altered in the presence of moderate liver metastases (i.e. 75% of liver volume replaced by the tumour). In these patients, there is no pharmacokinetic rationale for reducing vinorelbine doses.

In patients with massive liver metastases (i.e. >75% of liver volume replaced by the tumour), the real impact of impaired drug elimination capacity of the liver has not been characterised. In these patients, it is **empirically** suggested that the dose be reduced by 1/3 and the haematological toxicity closely followed-up.

Renal impairment

There is no pharmacokinetic rationale for reducing vinorelbine dose in patients with impaired kidney function.

The dose limiting toxicity of vinorelbine is mainly neutropenia. This usually occurs between day 8 and day 12 after administration of the medicinal product, is short-lived, and is not cumulative. If the neutrophil count is <2000/mm³ and/or platelet number is <75000/mm³, then the treatment should be delayed until recovery. Administration of the medicinal product is expected to be delayed by 1 week in about 35% of treatment courses.

The maximum tolerated dose per administration: 35.4 mg/m² body surface area

The maximum total dose per administration: 60 mg

The safety and efficacy in children and adolescents have not been demonstrated.

Special precautions for use and handling and disposal

The preparation and administration of vinorelbine should be carried out only by trained personnel. Suitable protective goggles, disposable gloves and disposable clothing must be worn. Spills and leakages must be wiped up.

Any contact with the eyes must be strictly avoided. If the solution does come into contact with the eyes they must be rinsed immediately with plenty of physiological saline.

After preparation, any exposed surface must be thoroughly cleaned and hands and face washed.

There is no incompatibility between the contents and container for VINOELBINE LINK and a neutral glass bottle, PVC bag, vinylacetate bag or infusion set with PVC tubes.

It is recommended to administer vinorelbine as an infusion over the course of 5-10 minutes after dilution in 20-50 ml physiological saline or glucose 50 mg/ml (5%) solution or by a short infusion (20-30 minutes) after dilution in 125 ml of normal saline or glucose 50 mg/ml (5%) solution. After administration the vein must be flushed through thoroughly with at least 250 ml isotonic solution.

Unused medicinal product and waste must be disposed of in accordance with local requirements.OVERDOSAGE

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 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 overdosage of vinorelbine given intravenously, symptomatic measures are necessary in case of an overdosage, 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 minimize 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

Immediately contact your doctor or the Poisons Information Centre should overdose occur (in Australia telephone 131 126)

PRESENTATION AND STORAGE CONDITIONS

VINORELBINE LINK is a clear, colorless to pale yellow solution in Water for Injections, containing 10 mg vinorelbine per mL.

VINORELBINE LINK is available in single-use, clear Type I glass vials with a fluoropolymer-coated bromobutyl rubber stopper, sealed with an aluminium crimp. The vials are individually packed in a carton in the following sizes:

- 10 mg/1 mL Single-Use Vial, Carton of 1 (AUST R 144030).
- 50 mg/5 mL Single-Use Vial, Carton of 1 (AUST R 144046).
- 10 mg/1 mL Single-Use Vial, Multiple pack of 10 vials (AUST R 144030).
- 50 mg/5 mL Single-Use Vial, Multiple pack of 10 vials (AUST R 144046).

Storage:

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

Shelf Life:

Unopened packaging: 24 months.

After dilution: Chemical and physical in use stability has been demonstrated for 24 hours at 2-8°C and at 25°C when stored in a PVC bag, PE bottle or glass bottle. To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If not used immediately, and if storage is necessary, hold at 2°-8°C for not more than 24 hours.

NAME AND ADDRESS OF THE SPONSOR

Link Medical Products Pty. Ltd.
18/6A Prosperity Parade
Warriewood NSW 2102
Australia

www.linkpharma.com.au

POSITION SCHEDULE OF THE MEDICINE

Vinorelbine is classified as Schedule 4.

DATE OF APPROVAL

TGA approval: *21 November 2008*