

NEW ZEALAND DATA SHEET

1 NAVELBINE® (10 MG/ML SOLUTION FOR INJECTION)

NAVELBINE® vinorelbine (as tartrate) 10 mg/mL solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL contains 10 mg vinorelbine (as tartrate).

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Solution for injection

NAVELBINE Injection is a clear colourless to pale yellow solution. The pH of NAVELBINE Injection is approximately 3.5.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

NAVELBINE Injection is indicated as a single agent or in combination for

1. the treatment of non small cell lung cancer (NSCLC), and
2. the second line treatment of advanced breast cancer

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults

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

In combination chemotherapy the dose may be the same and frequency of administration reduced, i.e. day 1 and 8 or day 1 and 5 every 3 weeks.

NAVELBINE Injection should be administered either by slow bolus over 6 to 10 minutes after dilution in 50 mL of a 0.9% sodium chloride 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 in patients with haematological toxicity

Neutrophil counts should be ≥ 1000 cells/mm³ prior to the administration of NAVELBINE Injection. Adjustments in the dosage of NAVELBINE Injection should be based on neutrophil counts obtained on the day of treatment (see Table 1).

Table 1.

Neutrophils (cells/mm ³) on Day of Treatment	Dose of NAVELBINE (mg/m ²)
≥ 1500	30
1000 TO 1499	15
< 1000	Do not administer**

**Repeat neutrophil count in 1 week. If three consecutive weekly doses are held because neutrophil count is < 1000 cells/mm³, discontinue NAVELBINE®.

Note:

For patients who, during treatment with NAVELBINE Injection, have experienced fever and/or sepsis while neutropenic or had 2 consecutive weekly doses withheld due to neutropenia, subsequent doses of NAVELBINE Injection should be:

22.5 mg/m² for neutrophils ≥ 1500 cells/mm³

11.25 mg/m² for neutrophils 1000 to 1499 cells/mm³

Dose modifications for hepatic insufficiency

NAVELBINE Injection should be administered with caution to patients with hepatic insufficiency. In patients who develop hyperbilirubinaemia during treatment with NAVELBINE Injection, the dose should be adjusted for total bilirubin (see Table 2):

Table 2. Dose Modification Based on Total Bilirubin

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

Dosage in patients with concurrent haematological toxicity and hepatic insufficiency

In patients with both haematologic toxicity and hepatic insufficiency, the lower of the doses from Tables 1 and 2 should be administered.

Dosage in Children

Safety and effectiveness have not been established.

Dosage in the Elderly

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

Administration Precautions

Caution – NAVELBINE Injection must be only administered intravenously through an infusion line. It is extremely important that the intravenous needle or catheter be properly positioned before any NAVELBINE Injection is injected. Leakage into surrounding tissue during intravenous administration of NAVELBINE 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 NAVELBINE Injection, institutional guidelines may be used.

As with other toxic compounds, caution should be exercised in handling and preparation of the solution of NAVELBINE Injection. Skin reactions may occur with accidental exposure. The use of gloves is recommended. If the solution of NAVELBINE Injection contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water. Severe irritation of the eye has been reported with accidental contamination of the eye with another vinca alkaloid. If this happens with NAVELBINE Injection, the eye should be flushed with water immediately and thoroughly.

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

NAVELBINE Injection is a clear, colourless to pale yellow solution. 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, NAVELBINE should not be administered.

Preparation for Administration

NAVELBINE Injection must be diluted in either a syringe or I.V. bag using one of the recommended solutions. The volume of dilution depends on the mode of administration:

- Bolus injection: 50 mL
- Infusion: 125 mL

Administration of NAVELBINE Injection must be followed with at least 250 mL of one of the solutions.

Diluted NAVELBINE Injection may be used for up to 24 hours under normal room light when stored in polypropylene syringes or polyvinyl chloride bags at 5° to 30°C.

Syringe

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

IV Bag

The calculated dose of NAVELBINE Injection should be diluted to a concentration between 0.5 and 2 mg/mL. The following solutions may be used for dilution: 5% Glucose Injection, USP; 0.9% Sodium Chloride Injection, USP; 0.45% Sodium Chloride Injection, USP; 5% Glucose and 0.45% Sodium Chloride Injection, USP; Ringer's Injection, USP; Lactated Ringer's Injection, USP.

After diluting NAVELBINE Injection 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.

NAVELBINE Injection should not be diluted in alkaline solutions due to the risk of precipitation.

NAVELBINE Injection should not be mixed with other agents. NAVELBINE Injection 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 2-8°C for not more than 24 hours.

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

4.3 CONTRAINDICATIONS

- Known hypersensitivity to vinorelbine or to any of the excipients or to other vinca alkaloids.
- Neutrophil count < 1500 cells/mm³, or severe infection, current or recent (within 2 weeks).
- Platelet count < 100,000 cells/mm³.
- Severe hepatic insufficiency.
- Pregnancy.
- Lactation (see section 4.6 Fertility, Pregnancy and Lactation).
- In combination with yellow fever vaccine (see section 4.5 Interactions with other medicines and other forms of interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Administration

NAVELBINE Injection should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. NAVELBINE Injection must only be administered by the intravenous route. Intrathecal administration of other vinca alkaloids has resulted in death. Improper administration of NAVELBINE Injection may result in extravasation causing local tissue necrosis and/or thrombophlebitis (see section 4.2, Dose modifications with haematological toxicity).

Myelosuppression

Patients treated with NAVELBINE Injection 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 NAVELBINE Injection 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 NAVELBINE Injection. NAVELBINE should not be administered to patients with neutrophil counts < 1500 cells/mm³ and/or platelet counts below 100,000 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 section 4.2 Dose and method of administration, Dose modifications for haematological toxicity).

NAVELBINE Injection 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 section 4.2 Dose and method of administration).

Respiratory system, thoracic and mediastinal disorders

Pulmonary toxicity, including severe acute bronchospasm, interstitial pneumonitis, acute respiratory distress syndrome (ARDS) occurring with use of NAVELBINE Injection intravenous pharmaceutical form has been reported. The mean time to onset of ARDS after vinorelbine administration was one week (range 3 to 8 days).

The infusion must be immediately interrupted in patients who develop unexplained dyspnea or have any evidence of pulmonary toxicity. NAVELBINE Injection must be permanently discontinued for confirmed interstitial pneumonitis.

Nervous system disorders

Peripheral Neuropathy

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

Autonomic Neuropathy

Treatment may be resumed after recovery of normal bowel motility.

General

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

Special care should be taken when prescribing for patients with a history of ischaemic heart disease. Patients presenting with ischaemic cardiac disease should be carefully monitored (see section 4.8 Undesirable effects).

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

Acute shortness of breath and severe bronchospasm have been reported infrequently following the administration of NAVELBINE 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 NAVELBINE Injection 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.

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

Use in hepatic impairment

There is no evidence that the toxicity of NAVELBINE Injection 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 NAVELBINE Injection. Because clinical experience in patients with severe liver disease is limited, caution should be exercised with administering NAVELBINE Injection to patients with severe hepatic injury or impairment.

Use in renal impairment

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

Paediatric use

Safety and effectiveness have not been established.

Effects on 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 NAVELBINE Injection.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Interactions common to all cytotoxics

Due to the increase of thrombotic risk in the case of tumoral diseases, the use of anticoagulative treatment is frequent. As the intra-individual variability of the coagulability during diseases is high and there is the risk of interaction between oral anticoagulants and anticancer therapy, if the patient is treated with oral anticoagulants, increasing the frequency of INR (International Normalised Ratio) monitoring is recommended.

Concomitant use contraindicated:

Yellow fever vaccine – risk of fatal generalised vaccine disease.

Concomitant use not recommended:

Live attenuated vaccines – risk of generalised vaccine disease, possibly fatal. This risk is increased in patients already immunodepressed by their underlying disease. The use of an inactivated vaccine where one exists is recommended (e.g. poliomyelitis);

Phenytoin – risk of exacerbation of convulsions resulting from the decrease in phenytoin absorption by the cytotoxic drug or loss of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin.

Concomitant use with caution:

Ciclosporin, 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 in their hepatic metabolism.

Concomitant use with caution:

Mitomycin - Acute pulmonary reactions have been reported with NAVELBINE Injection and other vinca alkaloids used in conjunction with mitomycin: risk of bronchospasm and dyspnoea are increased; in a rare case an interstitial pneumonitis was observed. NAVELBINE Injection should be administered with caution in combination with mitomycin.

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

Interactions specific to vinorelbine

The combination of NAVELBINE Injection with other drugs with known bone marrow toxicity is likely to exacerbate the myelosuppressive adverse effects.

Although the pharmacokinetics of vinorelbine are not influenced by the concurrent administration of cisplatin, the incidence of toxicities, specifically granulocytopenia, with the combination of NAVELBINE Injection and cisplatin is significantly higher than with single-agent NAVELBIN Injection E.

In studies with rats, the anticoagulant effect of phenindione was potentiated when given in combination with high dose 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.

Vinorelbine is metabolised by cytochrome CYP3A4. Although interaction studies have not been performed, it is expected that inhibitors of CYP3A4 such as ketoconazole, itraconazole, ritonavir etc. would result in elevated blood concentrations of vinorelbine. Inducers of CYP3A4 such as rifampicin and phenytoin may reduce concentrations of vinorelbine. Since the magnitude of the inducing or inhibiting effects is unknown, such drug combinations should be avoided.

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 the 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

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 - 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.

Men being treated with NAVELBINE Injection are advised not to father a child during and up to a minimum of 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 NAVELBINE Injection.

Pregnancy

Category D

NAVELBINE 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 embryonic deaths in mice. Doses causing adverse fetal effects in animals were lower than the human dose. There are no studies in pregnant women. If NAVELBINE

Injection 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 foetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with NAVELBINE Injection. Effective contraception must be used during treatment and up to 3 months after the treatment.

Lactation

It is not known whether vinorelbine is excreted in 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 NAVELBINE Injection, breast feeding must be discontinued before starting with NAVELBINE Injection.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effect of vinorelbine on the ability to drive and use machines has not been studied. However, patients should be advised not to drive or operate machinery if they experience any adverse reactions with a potential impact on their ability to perform these activities (e.g. dizziness and fatigue are common).

4.8 UNDESIRABLE EFFECTS

Adverse reactions reported are listed below, by MedDRA body system organ class and the following frequency convention : *very common* ($\geq 1/10$), *common* ($\geq 1/100, < 1/10$), *uncommon* ($\geq 1/1,000, < 1/100$), *rare* ($\geq 1/10,000, < 1/1,000$) and *very rare* ($< 1/10,000$).

Table 3. Tabulated list of adverse reactions

Infections and infestations	
Common:	Infection.
Uncommon:	Severe sepsis sometimes with other organ failure, septicaemia.
Very rare:	Complicated septicaemia, sometimes fatal.
Blood and lymphatic system disorders	
Very common:	Bone marrow depression resulting mainly in neutropenia. Neutropenia is the major dose-limiting toxicity with NAVELBINE Injection. Neutropenia (Grade 3: 24.3%, Grade 4: 27.8%) is rapidly reversible (7 to 14 days) and non-cumulative. It is maximal between 5 and 10 days after administration, depending on whether NAVELBINE Injection is used as single agent or in combination. Further treatment may be given after recovery of the neutrophil count. Anaemia (Grade 3 to 4: 7.4%). Dose adjustments are required for haematologic toxicity and hepatic insufficiency (see section 4.2).
Common:	Thrombocytopenia (Grade 3 to 4: 2.5%).
Endocrine disorders	
Uncommon:	Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Nervous system disorders	
Very common:	Mild to moderate peripheral neuropathy manifested by paraesthesia and loss of deep tendon reflexes (Grade 3:2.7%) and hyperesthesia have 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. Autonomic neuropathy: the main symptom is intestinal paresis causing constipation (Grade 3: 2%, Grade 4: 0.6%).
Uncommon:	Severe paresthesias with infrequent sensory and motor symptoms.
Gastrointestinal disorders	
Very common:	Stomatitis, constipation (see Nervous system disorders), - Nausea and vomiting (G 1-2: 30.4% and G 3-4: 2.2%). Anti-emetic therapy may reduce their occurrence.
Common:	Diarrhoea, usually mild to moderate, may occur.
Rare:	Pancreatitis, paralytic ileus, treatment may be resumed after recovery of normal bowel mobility
Skin and subcutaneous tissue disorders	
Very common:	Alopecia is mild and may appear progressively with extended courses of treatment.
Rare:	Generalised cutaneous reactions.
Hepatobiliary disorders	
Very common:	Transient elevations of liver enzymes were reported without clinical symptoms.
Respiratory, thoracic and mediastinal disorders	
Common:	Shortness of breath was reported in 3% of patients. NAVELBINE Injection, like other vinca alkaloids, may produce bronchospasm.
Rare:	Interstitial pneumopathy (in particular, in combination with mitomycin), sometimes fatal.
Cardiovascular 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:	Myocardial infarction, angina pectoris and/or transient electrocardiogram changes have been reported (see section 4.4 Special warnings and precautions for use).
Very rare:	Cardiac failure and pulmonary oedema have been reported during treatment with NAVELBINE Injection, however a causal relationship has not been established. Tachycardia, palpitation and heart rhythm disorders.
Vascular disorders	
Uncommon:	Hypotension, hypertension, flushing and peripheral coldness.
Rare:	Severe hypotension and collapse are rare.
Musculoskeletal and connective tissue disorders	
Common:	Jaw pain, myalgia, arthralgia.
Renal and urinary disorders	
Uncommon:	Haemorrhagic cystitis.
Metabolism and nutrition disorders	
Rare:	Severe hyponatraemia.
General disorders and administration site conditions	
Very common:	Like other anticancer vinca alkaloids, NAVELBINE Injection is a moderate vesicant. Reactions at the injection site including erythema, pain and vein discolouration occurred in approximately one-third of patients (5% were severe). Chemical phlebitis along the vein proximal to the site of injection were reported in 10% of patients.

	Fatigue occurred in 27% of patients. It was usually mild or moderate but tended to increase with cumulative dosing.
Common:	Pain at the tumour site, rash, chest pain of non-cardiac origin, asthenia, fever.
Rare:	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.

Table 4. Adverse Events Observed in Pivotal Phase III studies

	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
- Leukopenia				
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
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

	Total NAVELBINE %	Total NAVELBINE combined* %	VDS + CDDP %	5 FU + LV %
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

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

VDS = vindesine

CDDP = cisplatin

LV = leucovorin

Post-Marketing Experience

The following additional adverse reactions have been reported from post marketing experience and clinical trials according to the MedDRA classification with the frequency 'not known'. The reactions were described using CTCAE classification which provide a terminology for AE's and a grading scale of the severity of AEs (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).

Table 5. Adverse reactions have been reported from post marketing experience

Infections and infestations	Neutropenic sepsis. Neutropenic infection G3-4
Blood and lymphatic system disorders	Febrile neutropenia, pancytopenia, leucopenia G1-4
Immune system disorders	Systemic allergic reactions including anaphylaxis, anaphylactic shock or anaphylactoid type reactions.
Metabolism and nutrition disorders	Anorexia.
Skin and subcutaneous tissue disorders	Palmer-plantar erythrodysesthesia syndrome.
Nervous system disorders	Headache, dizziness, ataxia
Cardiac disorders	Heart failure
Respiratory system	Cough G1-2

	Acute respiratory distress syndrome (ARDS) sometimes fatal (see Section 4.4 Special warnings and precautions for use).
Gastrointestinal disorders	Gastrointestinal bleeding, severe diarrhoea, abdominal pain
Hepatobiliary disorders	Hepatic disorders
General disorders	Chills G1-2
Investigations	Weight loss

For the oral formulation of NAVELBINE the following additional adverse reactions were reported: neuromotor disorders, taste disorder, visual impairment, insomnia, dysphagia, oesophagitis, weight gain, dysuria, other genitourinary symptom.

Reporting of suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 OVERDOSE

There is no known antidote for overdoses of NAVELBINE Injection. 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, growth factors and antibiotics should be instituted as deemed necessary by the physician.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Vinca alkaloids and analogues (ATC Code: L01C A04)

Physicochemical properties

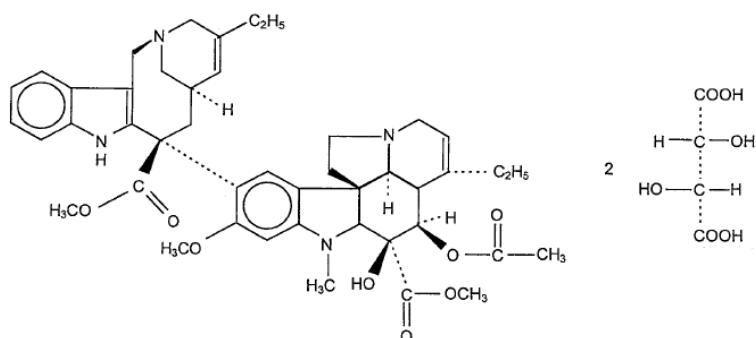
Vinorelbine tartrate is a semi-synthetic vinca alkaloid with antitumor activity.

The chemical name is 3',4'-didehydro-4'-deoxy-C'-norvincal leukoblastine [R-(R*,R*)-2,3 dihydroxybutanedioate (1:2)(salt)].

Vinorelbine tartrate is a white to yellow or light brown amorphous powder with the molecular formula $C_{45}H_{54}N_4O_8 \cdot 2C_4H_6O_6$ and molecular weight of 1079.12. The aqueous solubility is > 1000 mg/mL in distilled water.

Vinorelbine tartrate has the following structure:

Chemical structure



CAS number

125317-39-7

Mechanism of action

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 μM), including a blockade of cells at metaphase. Vincristine produced depolymerisation of axonal tubules at 5 μM , but vinblastine and vinorelbine did not have this effect until concentrations of 30 μM and 40 μM 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 human: its toxicity and activity are slightly higher than those of vinorelbine.

Clinical efficacy and safety

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 14-45% (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% (patient weighted average = 30.9%) and median survival was 24-82 weeks.

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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 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 treatment of advanced breast cancer. Results from trials are summarised in the following Table 6.

Table 6.

Agent	No. 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%

Non-small cell lung cancer

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-naïve patients. The high activity of vinorelbine as single agent in non-small cell lung cancer which was observed in non-controlled 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 5-fluorouracil with leucovorin (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 5-fluorouracil/leucovorin arm (log-rank p=0.03). The response rates were 12% for the vinorelbine arm and 3% for the fluorouracil/leucovorin 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 (30mg/m²/week), vinorelbine (30mg/m²/week) cisplatin (120 mg/m² days 1 and 29 then every 6 weeks), and vindesine (3mg/m²/week for 7 weeks, then every second week) plus cisplatin (120 mg/m² days 1 and 29 then every 6 weeks). Vinorelbine plus cisplatin produced longer survival times than vindesine plus cisplatin (median survival 40 weeks vs 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 vs 32 weeks). The 1-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.

5.2 PHARMACOKINETIC PROPERTIES

Distribution

Following intravenous administration of NAVELBINE Injection to patients at 30 mg/m², 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.

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, 5-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.

Biotransformation

One active metabolite, deacetylvinorelbine, has been detected but not quantified in human plasma.

Elimination

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 undergoes substantial hepatic elimination in humans, with large amounts recovered in faeces after intravenous administration to humans.

Hepatic impairment

Dose adjustments are recommended for patients with impaired hepatic function (see section 4.2 Dose and method of administration).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity studies in mice and rats showed no tumourigenic activity at dose levels up to 2.4 mg/m² given by IV 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

NAVELBINE Injection also contains water for injections.

6.2 INCOMPATIBILITIES

Refer to section 4.2 Dose and method of administration, Preparation for administration.

6.3 SHELF LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

6.5 NATURE AND CONTENTS OF CONTAINER

NAVELBINE Injection is available in single-use, clear glass vials with black or grey elastomeric stoppers and royal blue caps, individually packaged in a carton in the following vial sizes:

10 mg/1 mL Single-Use Vial, Cartons of 1 and 10

50 mg/5 mL Single-Use Vial, Cartons of 1 and 10

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

New Zealand Medical & Scientific Limited
PO Box 24-138,
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AUCKLAND
Ph (09) 259 4062
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9 DATE OF FIRST APPROVAL

11 June 1998

10 DATE OF REVISION OF THE TEXT

21 August 2020

Summary table of changes

Section changed	Summary of new information
4.4	Update to include additional respiratory system precautions to comply with CCDS Version 10.0
4.8	Update to additional AE's to comply with CCDS Version 10.0.
All	Editorial changes including references to section of DS and update of product name to include dosage form for consistency throughout the DS.