AUSTRALIAN PRODUCT INFORMATION – NAVELBINE® INJECTION (VINORELBINE TARTRATE) CONCENTRATED INJECTION

1 NAME OF THE MEDICINE

Vinorelbine tartrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL contains 10 mg vinorelbine (as tartrate) and each 5 mL contains 50 mg vinorelbine (as tartrate).

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

3 PHARMACEUTICAL FORM

Concentrated injection

NAVELBINE Injection is a clear, colourless to pale yellow solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

NAVELBINE is indicated for the 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.

NAVELBINE is indicated for the treatment, in combination with cisplatin, of patients with completely resected non-small cell lung cancer of stage IB or greater.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults

Advanced Breast Cancer and Non-Small Cell Lung Cancer

- Single agent treatment is usually given at 25-30 mg/m^2 weekly intravenously.
- In combination chemotherapy the dose may be the same and the frequency of administration reduced, ie: day 1 and 8 or day 1 and 5 every 3 weeks.

Resected Non-Small Cell Lung Cancer (Stage IB or Greater)

In combination with cisplatin for treatment of patients with completely resected non-small cell lung cancer (Stage IB or greater), NAVELBINE may be administered at an initial dose of 25-30 mg/m^2 intravenously at weekly intervals for 16 weeks. The dose of cisplatin is 100 mg/m^2 administered intravenously over 1 hour, on days 1, 29, 57 and 85.

- NAVELBINE should be administered either by infusion over 6 to 10 minutes after dilution in 50 mL of a normal saline solution or by a 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 and prevent phlebitis. NAVELBINE is a moderate vesicant. Insertion of a central venous line may be necessary (see section 4.8 Adverse effects (Undesirable effects), Dermatological).

Dose modifications for haematological toxicity

Advanced Breast Cancer and Non Small Cell Lung Cancer

Neutrophil counts should be ≥ 1 x 10^9 cells/L prior to the administration of NAVELBINE. Adjustments in the dosage of NAVELBINE should be based on neutrophil counts obtained on the day of treatment (see Table 1).

Table 1.

Neutrophils (cells x 10^9/L) on Day of Treatment	**Dose of NAVELBINE (mg/m^2)**
≥ 1.5	30
1 to 1.499	15
< 1	Do not administer. Repeat neutrophil count in 1 week. If three consecutive weekly doses are withheld because neutrophil count is < 1 x 10^9 cells/L, discontinue NAVELBINE**.**

Note: for patients who, during treatment with NAVELBINE, have experienced fever and/or sepsis while neutropenic or had 2 consecutive weekly doses withheld due to neutropenia, subsequent doses of NAVELBINE should be: 22.5 mg/m^2 for neutrophils ≥ 1.5 x 10^9 cells/L; 11.25 mg/m^2 for neutrophils 1 x 10^9 to 1.499 x 10^9 cells/L.

Resected Non Small Cell Lung Cancer

If the neutrophil count falls below 1 x 10^9 cells/L and/or the platelet count falls below 100 x 10^9 cells/L, the dose should be delayed by 1 week, with reassessment of neutrophil and platelet counts until recovery. If treatment cannot be given after a three week interval, because of haematological toxicity, treatment should be discontinued.

Dose modifications for hepatic insufficiency

For patients presenting with severe liver impairment (bilirubin > 2xUNL and/or transaminases > 5xUNL), it is suggested that the dose be reduced by 33% and the haematological parameters closely monitored since the maximum dose which was evaluated in this subset of patients was 20 mg/m^2.

Administration precautions

Caution - NAVELBINE 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 is infused. Leakage into surrounding tissue during intravenous administration of NAVELBINE may cause considerable irritation, local tissue necrosis, and/or thrombophlebitis.

If extravasation occurs, the infusion 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, institutional guidelines may be used.

As with other toxic compounds, caution should be exercised in handling and preparation of the solution of NAVELBINE. Skin reactions may occur with accidental exposure. The use of gloves is recommended. If the solution of NAVELBINE 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, 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 discolouration prior to administration whenever solution and container permit. If particulate matter is seen, NAVELBINE should not be administered.

NAVELBINE is for intravenous use by infusion only. Fatal if given by any other route.

Preparation for Administration

NAVELBINE Injection must be diluted in an I.V. bag using one of the recommended solutions. The volume of dilution is 125 mL.

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

Diluted NAVELBINE may be used for up to 24 hours under normal room light when stored inpolyvinyl chloride bags at 5° to 30°C.

Syringes should not be used for NAVELBINE administration. Preparation must be by dilution in small volume intravenous bags (the ‘minibag’ technique), rather than in a syringe, to protect against accidental administration via a spinal route.

The calculated dose of NAVELBINE 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 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 should not be diluted in alkaline solutions due to the risk of precipitation.

NAVELBINE should not be mixed with other agents. NAVELBINE 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/mm^3, or severe infection, current or recent (within 2 weeks).
- Platelet count < 100,000 cells/mm^3.
- Severe hepatic insufficiency.
- Pregnancy.
- Lactation.
- In combination with yellow fever vaccine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Administration

NAVELBINE is for intravenous use by infusion only. Fatal if given by any other route.

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 may result in extravasation causing local tissue necrosis and/or thrombophlebitis (see section 4.2 Dose and method of administration, Administration precautions).

Myelosuppression

Patients treated with NAVELBINE 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 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. NAVELBINE should not be administered to patients with neutrophil counts < 1500 cells/mm^3 and/or platelet counts below 100,000 cells/mm^3. 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 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 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 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 are reversible. If severe adverse events occur, NAVELBINE should be reduced in dosage or discontinued and appropriate corrective measures taken. Reinstitution of therapy with NAVELBINE 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 Adverse effects (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 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 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 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. Because clinical experience in patients with severe liver disease is limited, caution should be exercised with administering NAVELBINE 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 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 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 with strong modulators of this membrane transporter.

Interactions specific to vinorelbine

The combination of NAVELBINE 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 and cisplatin is significantly higher than with single-agent NAVELBINE.

In studies with rats, the anticoagulant effect of phenindione was potentiated when given in combination with a high dose of vinorelbine (30 mg/m^2/day for 4 consecutive days or

15 mg/m^2/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/m^2 when combined with daily lapatinib 1000 mg. This type of combination should be administered with caution.

4.6 FERTILITY, PREGNANCY AND LACTATION

Contraception in males and females

Women of childbearing potential should be advised to avoid becoming pregnant during therapy with NAVELBINE. Effective contraception must be used during treatment and for 7 months after the treatment.

Men being treated with NAVELBINE are advised not to father a child during and for a minimum of 4 months after treatment. Men must use effective contraception during treatment and for 4 months after treatment.

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 – 7.2 mg/m^2 for 13 weeks, reduced prostate/seminal vesicle secretion in rats dosed twice weekly at 3 mg/m^2 for 26 weeks, reduced testicular weight in mice dosed at 19 mg/m^2/day for three 5-day cycles and reduced epididymal weight in dogs dosed at 5 mg/m^2 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/m^2 once weekly or up to 4.2 mg/m^2 at 3-day intervals) were lower than the human dose.

Prior to treatment of male patients, advice should be sought for conserving sperm due to the chance of irreversible infertility as a consequence of treatment with NAVELBINE.

Use in 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/m^2 respectively. A single 9 mg/m^2 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 NAVELBINE 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.

Use in 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/m^2 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, breast feeding must be discontinued before starting treatment with NAVELBINE.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse reactions reported are listed below, by MedDRA body system organ class and the following frequency convention: *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).*

Table 2. 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; anaemia.
Common:	Thrombocytopenia.
Endocrine disorders	
Uncommon:	Syndrome of inappropriate antidiuretic hormone secretion (SIADH).
Nervous system disorders	
Very 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.
Uncommon:	Severe paresthesias with infrequent sensory and motor symptoms.
Gastrointestinal disorders	
Very Common:	Stomatitis, nausea and vomiting, constipation (see Nervous system disorders).
Common:	Diarrhoea, severe nausea and vomiting.
Rare:	Pancreatitis, paralytic ileus.

Skin and subcutaneous tissue disorders	
Very Common:	Alopecia
Common:	Severe injection site reactions.
Rare:	Generalised cutaneous reactions, tissue necrosis at injection site.
Hepatobiliary disorders	
Very Common:	Transient elevations of liver enzymes.
Respiratory, thoracic and mediastinal disorders	
Common:	Shortness of breath, bronchospasm.
Rare:	Interstitial pneumopathy (in particular, in combination with mitomycin), sometimes fatal
Cardiovascular disorders	
Common:	Chest pain.
Rare:	Myocardial infarction, angina pectoris, transient electrocardiogram changes.
Very rare:	Cardiac failure, pulmonary oedema, tachycardia, palpitation and heart rhythm disorders.
Vascular disorders	
Uncommon:	Hypotension, hypertension, flushing and peripheral coldness.
Rare:	Severe hypotension, collapse.
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:	Reactions at the injection site including erythema, pain, vein discolouration and local phlebitis. Fatigue.
Common:	Pain at the tumour site, chest pain of non-cardiac origin, asthenia, fever
Rare:	Local necrosis.

Table 3. 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

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

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

Table 4. 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
Anaemia	77.7	6.1
Thrombocytopenia	14.3	0.5
Cardiac disorders		
Cardiac failure	4.3	2.6
Pericarditis	0.3	1
Sinus tachycardia	7.2	2.6
Ventricular extrasystoles	2.3	1.8
Gastrointestinal disorders		
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 disorders and administration site conditions		
Asthenia	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 disorders		
Anorexia	70.8	17.3
Nervous system disorders		
Neuropathy peripheral	28.4	1.0
Respiratory, thoracic and mediastinal disorders		
Dyspnoea at rest	1.7	2.9
Dyspnoea 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	-

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 Skin hyperpigmentation (Serpentine Supravenous Hyperpigmentation)
Nervous system disorders	Headache, dizziness, ataxia, posterior reversible encephalopathy syndrome
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) Pulmonary embolism
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 suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no known antidote for overdoses of NAVELBINE. 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 information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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 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-naive 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.

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/m^2, 9 doses and 12 weeks respectively and for melphalan, 25 mg/m^2, 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 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

Advanced

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 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 (30 mg/m^2/week), vinorelbine (30 mg/m^2/week), cisplatin (120 mg/m^2 days 1 and 29 then every 6 weeks), and vindesine (3 mg/m^2/week for 7 weeks, then every second week) plus cisplatin (120 mg/m^2 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.

Resected (Stage IB or greater)

In a large phase III, open-label, multicenter, comparative, randomized study, 840 patients with resected primary NSCLC stage I (T2N0 only), II, IIIA and ECOG/WHO performance status < 2, were randomised to treatment with a combination of IV vinorelbine (30 mg/m^2 on days 1, 8, 15, 22 with a maximum of 16 administrations in 20 weeks) and Cisplatin (100 mg/m^2 on days 1, 29, 57, 85) or observation alone, i.e. no chemotherapy. Vinorelbine in combination with cisplatin significantly prolongs survival of patients with completely resected NSCLC in comparison with observation alone (see Table 7).

Adjuvant Vinorelbine and Cisplatin after NSCLC Resection

Table 7. European ANITA 01 Trial – Intent-to-Treat

	Vinorelbine + Cisplatin n=407	**Observation n=433**	**Hazard Ratio [95% CI]**
Disease-Free Survival[1] *median yrs*	3.0	1.7	0.76 [0.64, 0.91]
Survival *median yrs*	5.5	3.6	0.80 [0.66, 0.96]
Follow-up median *(range) yrs*	6.4 (3.6-9.7)	6.4 (3.6-9.7)	

[1]Time from randomisation to relapse or death from any cause.

A supporting trial of similar design in 482 patients used a lower dose of vinorelbine - 25 mg/m^2 weekly for 16 weeks – and a different schedule of cisplatin administration - 50 mg/m^2 on days 1 and 8 every 4 weeks for 4 cycles – than the pivotal trial and achieved a similar survival advantage (hazard ratio 0.69, 95% confidence interval 0.52, 0.91) to the pivotal trial. The patients had better prognosis than those in the pivotal trial since only patients with stage IB and II disease were enrolled and ECOG performance status was 0-1. It was noteworthy that the vinorelbine dose had been reduced from 30 mg/m^2 to 25 mg/m^2 after the first 18 patients because of haematological toxicity.

5.2 PHARMACOKINETIC PROPERTIES

Distribution

Following intravenous administration of NAVELBINE 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.

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.

Metabolism

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

Excretion

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/m^2 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 also contains the following excipients: water for injections. The pH of NAVELBINE® Injection is approximately 3.5.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

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

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

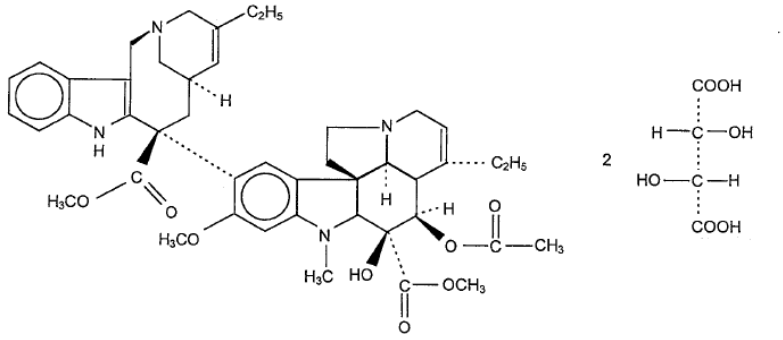
6.7 PHYSICOCHEMICAL PROPERTIES

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

The chemical name is 3',4'-didehydro-4'-deoxy-C'-norvincaleukoblastine [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 $C_{45}H_{54}N_4O_8$. $2C_4H_6O_6$ and a molecular weight of 1079.12. The aqueous solubility is > 1000 mg/mL in distilled water.

Chemical structure



CAS number

125317-39-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

(S4) Prescription Only Medicine

8 SPONSOR

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Australia

9 DATE OF FIRST APPROVAL

16 February 1998

10 DATE OF REVISION

21 May 2025

Summary table of changes

Section changed	Summary of new information
4.6	Extension of timeframe for men and women to use contraception post treatment