

AUSTRALIAN PRODUCT INFORMATION – NAVELBINE® (VINORELBINE TARTRATE) SOFT CAPSULES

1 NAME OF THE MEDICINE

Vinorelbine tartrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Capsules contain 20 mg, 30 mg and 80 mg vinorelbine (as tartrate).

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

3 PHARMACEUTICAL FORM

Soft capsule

20 mg soft capsule: light brown soft capsule printed N20.

30 mg soft capsule: pink soft capsule printed N30.

80 mg soft capsule*: pale yellow soft capsule printed N80.

*Not marketed

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Non-small cell lung cancer

NAVELBINE Oral is indicated for the first line treatment of advanced non-small cell lung cancer, as a single agent or in combination.

Breast cancer

NAVELBINE Oral is indicated for the treatment of advanced breast cancer after failure of standard therapy as a single agent or in combination.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults

Single agent

The recommended regimen is:

First three administrations: 60 mg/m², administered once weekly.

Subsequent administrations:

Beyond the third administration, increasing the dose of NAVELBINE Oral to 80 mg/m² once weekly is recommended, except in those patients for whom the neutrophil count has dropped once below 500/mm³ or more than once between 500 and 1000/mm³ during the first 3 administrations at 60 mg/m².

Dose modifications according to haematological status

If the neutrophil count is below 1500/mm³ and/or the platelet count is below 100,000/mm³, then treatment should be delayed until recovery.

Table 1.

Neutrophil count during the first 3 administrations at 60 mg/m ² /week	Neutrophils >1000	Neutrophils ≥500 and <1000 (1 episode)	Neutrophils ≥500 and <1000 (2 episodes)	Neutrophils <500
Recommended dose for 4 th and subsequent administrations	80	80	60	60

For any administration planned at the 80 mg/m²/week dose, if the neutrophil count falls below 500/mm³ or more than once between 500 and 1000/mm³, the dose must be delayed until recovery and reduced from 80 to 60 mg/m² per week during the 3 subsequent administrations.

Table 2.

Neutrophil count beyond the 4 th administration at 80 mg/m ² /week.	Neutrophils >1000	Neutrophils ≥500 and < 1000 (1 episode)	Neutrophils ≥500 and < 1000 (2 episodes)	Neutrophils <500
Recommended dose for the next administration.	80		60	

It is possible to re-escalate the dose from 60 to 80 mg/m²/week if the neutrophil count does not drop below 500/mm³, or more than once between 500 and 1000/mm³ during the three administrations given at the 60 mg/m² dose.

Dose modification for hepatic impairment

Vinorelbine is contraindicated in patients with severe hepatic impairment. In patients with moderate hepatic impairment (serum bilirubin between 1.5 and 3 x ULN, independent of ALT and AST concentrations), NAVELBINE Oral monotherapy should be administered at a dose of 50 mg/m²/week. In patients with mild hepatic impairment (serum bilirubin <1.5 x ULN and ALT and/or AST between 1.5 and 2.5 x ULN), NAVELBINE Oral may be

administered at the standard dose of 60 mg/m²/week. Haematological toxicity should be closely monitored. Hepatic impairment has not been studied in combination chemotherapy.

Combination chemotherapy

General

The use of oral vinorelbine in combination regimens has not been extensively studied. However, based on pharmacokinetic studies, the oral dose of 80 mg/m² was demonstrated to correspond to 30 mg/m² of the IV form and 60 mg/m² orally to 25 mg/m² IV.

In combination regimens, intravenous vinorelbine dosing may be replaced with oral vinorelbine therapy. The recommended dose is 60 mg/m². The safety of higher doses of oral vinorelbine (e.g. 80 mg/m²) in combination regimens has not been established, except for use with capecitabine in advanced breast cancer (see below).

Combination with Capecitabine in Advanced Breast Cancer

In combination with capecitabine for the treatment of advanced breast cancer, the administration of NAVELBINE Oral is recommended on days 1 and 8 for three week cycles at 60 mg/m² for the first cycle, then increased to 80 mg/m² for subsequent cycles, except in patients for whom the neutrophil count has dropped below 500/mm³ or more than once between 500 and 1000/mm³ during the first administration at 60 mg/m². Capecitabine should be administered at a dose of 1000 mg/m², twice daily on Days 1-14 of the three week cycle.

The following table gives the dose required for appropriate ranges of body surface area (BSA).

Table 3.

BSA (m²)	60 mg/m² Dose (mg)	80 mg/m² Dose (mg)
0.95 to 1	60	80
1.05 to 1.14	70	90
1.15 to 1.24	70	100
1.25 to 1.34	80	100
1.35 to 1.44	80	110
1.45 to 1.54	90	120
1.55 to 1.64	100	130
1.65 to 1.74	100	140
1.75 to 1.84	110	140
1.85 to 1.94	110	150
≥ 1.95	120	160

Even for patients with a body surface area (BSA) ≥ 2 m², the dose should never exceed 120 mg per week at 60 mg/m² and 160 mg per week at 80 mg/m².

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

Method of administration

NAVELBINE Oral must be given strictly by the oral route. They should be swallowed whole with water and should not be chewed or sucked. It is recommended that the capsule be taken with food.

4.3 CONTRAINDICATIONS

- Known hypersensitivity to vinorelbine or to other vinca alkaloids or to any of the excipients listed in section 6.1 List of excipients.
- Disease significantly affecting absorption.
- Previous significant surgical resection of stomach or small bowel.
- Neutrophil counts < 1500 cells/mm³, or current or recent severe infection due to neutropenia (within 2 weeks).
- Platelet count $< 100,000$ cells/mm³.
- Pregnancy.
- Lactation (see section 4.6 Fertility, Pregnancy and Lactation).
- Patients requiring long-term oxygen therapy.
- Severe hepatic insufficiency.
- 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 Oral should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents with facilities for monitoring cytotoxic drugs.

If the patient chews or sucks the capsule by mistake, rinse mouth with water or preferably a normal saline solution. In the event of the capsule being cut or damaged, the liquid content is an irritant, and so may cause damage if in contact with skin, mucosa or eyes. Damaged capsules should not be swallowed and should be returned to the pharmacy or to the physician in order to be properly destroyed. If any contact occurs, immediate thorough washing with water or preferably with normal saline solution should be undertaken.

If vomiting occurs within a few hours of drug intake, administration of the dose should not be repeated. Prophylactic treatment such as 5HT₃ antagonists (e.g. ondansetron, granisetron) may reduce the incidence. NAVELBINE Oral is associated with a higher incidence of nausea/vomiting than the i.v formulation. A primary prophylaxis with antiemetics is recommended. It is recommended that the capsule be taken with food.

Constipation is a very common gastrointestinal disorder. The prescription of laxatives may be appropriate for patients with a prior history of constipation and/or are receiving concomitant treatment with opiates.

Myelosuppression

Neutropenia is dose-limiting. Complete blood counts with differentials should be performed and results reviewed prior to administering each dose of NAVELBINE Oral. Patients treated with NAVELBINE Oral should be frequently monitored for myelosuppression both during and after therapy. NAVELBINE Oral 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 modification for haematological toxicity).

NAVELBINE Oral 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).

During clinical trials, where treatment was initiated at a weekly dose of 80 mg/m² (corresponding to an IV dose of 30 mg/m² in terms of systemic exposure), febrile neutropenia, in some cases fatal, was encountered in about 15% of patients. Therefore, it is recommended that the starting dose should be 60 mg/m² and increased to 80 mg/m² only if the dose is tolerated (see section 4.2 Dose and method of administration).

General

Most drug-related adverse events of NAVELBINE Oral are reversible. If severe adverse events occur, NAVELBINE Oral should be reduced in dosage or discontinued and appropriate corrective measures taken. Reinstitution of therapy with NAVELBINE Oral 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;
- with poor performance status.

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 along with rare cases of interstitial pneumopathy 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.

Due to the presence of sorbitol, patients with the rare hereditary problem of fructose intolerance should not take this medicine.

NAVELBINE Oral contains small amounts of ethanol (alcohol), less than 100 mg per dose. The small amount of alcohol in this medicine will not have any noticeable effects.

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

Use in hepatic impairment

Vinorelbine is contraindicated in patients with severe hepatic impairment. In patients with moderate hepatic impairment (serum bilirubin between 1.5 and 3 x ULN, independent of ALT and AST concentrations), dose reduction is recommended (see section 4.2 Dose and method of administration). In patients with mild hepatic impairment (serum bilirubin <1.5 x ULN and ALT and/or AST between 1.5 and 2.5 x ULN), no dose reduction is required. Haematological toxicity should be closely monitored.

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. Use in children and adolescents aged <18 years is therefore not recommended.

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 Oral. If the neutrophil count is below 1500/mm³ and/or the platelet count is below 100,000/mm³, then treatment should be delayed until recovery.

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 Oral 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 Oral and other drugs with known bone marrow toxicity is likely to exacerbate the myelosuppressive adverse effects.

In the absence of specific studies evaluating drug-drug interaction with warfarin, the patient should be cautiously monitored when vinorelbine is given in combination with warfarin.

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 Oral and cisplatin is significantly higher than with single-agent NAVELBINE Oral.

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

Food

Simultaneous intake of a low fat standard meal does not modify exposure to vinorelbine.

4.6 FERTILITY, PREGNANCY AND LACTATION

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/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 Oral 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 Oral.

Use in pregnancy – Category D

NAVELBINE Oral may cause foetal 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 foetal effects in animals were lower than the human dose. There are no studies in pregnant women. If NAVELBINE Oral 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 Oral. Effective contraception must be used during treatment and up to 3 months after the treatment.

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/m² every three days. Because many drugs are excreted in human milk and because of the potential serious adverse reactions in nursing infants from NAVELBINE Oral, breast-feeding must be discontinued in women before starting treatment with NAVELBINE Oral.

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)

The overall reported incidence of adverse effects was determined from clinical studies in 316 patients (132 patients with non-small cell lung cancer and 184 patients with breast cancer) who received the recommended regimen of NAVELBINE (first three administrations at 60 mg/m²/week followed by 80 mg/m²/week).

Adverse reactions reported are listed below by MedDRA body system organ class and the frequency convention.

Frequency of adverse reactions is defined as: very common ($\geq 1/10$); common ($\geq 1/100$ and $< 1/10$); uncommon ($\geq 1/1000$ and $< 1/100$); rare ($\geq 1/10,000$ and $< 1/1000$) and very rare ($< 1/10,000$). Additional adverse reactions pooled from post-marketing experience and clinical trials have been added according to the MedDRA classification with the frequency 'Not known'.

The reactions were described using the Common Terminology Criteria for Adverse Events (CTCAE) classification which provides a terminology for adverse events (Aes) and a grading scale 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).

Adverse effects reported with NAVELBINE Oral

Pre-marketing experience

The most commonly reported adverse drug reactions are bone marrow depression with neutropenia, anaemia and thrombocytopenia, gastrointestinal toxicity with nausea, vomiting, diarrhoea, stomatitis and constipation. Gastrointestinal adverse events occur more commonly with oral vinorelbine than with intravenous administration. Fatigue and fever were also very commonly reported.

Post-marketing experience

NAVELBINE Oral is used as a single agent or in combination with other chemotherapeutic agents or targeted therapy agents such as cisplatin or capecitabine. The most common system organ classes involved from post-marketing experience are: ‘blood and lymphatic system disorders’, ‘gastrointestinal disorders’, ‘infections and infestations’ and ‘general disorders and administration site conditions’. This information is consistent with pre-marketing experience.

Table 4. Adverse effects reported of NAVELBINE Oral

Infections and infestations	
Very common:	Bacterial, viral or fungal infections without neutropenia at different sites: G1-4: 12.7%; G3-4: 4.4%.
Common:	Bacterial, viral or fungal infections resulting from bone marrow depression and/or immune system compromise (neutropenic infections). Usually reversible with an appropriate treatment. Neutropenic infection: G3-4: 3.5%.
Not known:	Neutropenic sepsis Complicated septicaemia, sometimes fatal Severe sepsis sometimes with other organ failure Septicemia.
Blood and lymphatic system disorders	
Very common:	Bone marrow depression resulting mainly in neutropenia: G1-4: 71.5%; G3: 21.8%; G4: 25.9%, is reversible and is the dose limiting toxicity. Leucopenia: G1-4: 70.6%; G3: 24.7%; G4: 6%, Anaemia: G1-4: 67.4%; G3-4: 3.8%. Thrombocytopenia: G1-2: 10.8%.
Common:	Neutropenia associated with fever over 38°C including febrile neutropenia: G4: 2.8%.
Not known:	Thrombocytopenia G3-4 Pancytopenia.
Endocrine Disorders	
Not known	Inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	
Very common	Anorexia: G1-4: 38.6%; G3-4: 4.1%.
Not known:	Severe hyponatraemia
Psychiatric disorders	
Common:	Insomnia: G1-2: 2.8%.
Nervous system disorders	
Very common:	Neurosensory disorders: G1-2: 11.1% were generally limited to loss of tendon reflexes and infrequently severe.
Common:	Neuromotor disorders: G1-4: 9.2%; G3-4: 1.3%. Headache: G1-4: 4.1%; G3-4: 0.6%. Dizziness: G1-4: 6%; G3-4: 0.6%. Taste disorders: G1-2: 3.8%.
Uncommon:	Ataxia: G3: 0.3%.
Eye disorders	
Common:	Visualimpairment: G1-2: 1.3%.

Cardiac disorders	
Uncommon:	Heart failure and cardiac dysrhythmia.
Not known:	Myocardial infarction in patients with cardiac medical history or cardiac risk factors.
Vascular disorders	
Common:	Hypertension: G1-4: 2.5%; G3-4: 0.3%. Hypotension: G1-4: 2.2%; G3-4: 0.6%.
Respiratory, thoracic and mediastinal disorders	
Common:	Dyspnoea: G1-4: 2.8%; G3-4: 0.3%. Cough: G1-2: 2.8%.
Gastrointestinal disorders	
Very common:	Nausea: G1-4: 74.7%; G3-4: 7.3%. Vomiting: G1-4: 54.7%; G3-4: 6.3%. Diarrhoea: G1-4: 49.7%; G3-4: 5.7%. Stomatitis: G1-4: 10.4%; G3-4: 0.9%. Abdominal pain: G1-4: 14.2%. Constipation: G1-4: 19%; G3-4: 0.9%. Gastric disorders: G1-4: 11.7%.
Common:	Oesophagitis: G1-3: 3.8%; G3: 0.3%. Dysphagia: G1-2: 2.3%.
Uncommon:	Paralytic ileus: G3-4: 0.9% (exceptionally fatal) treatment may be resumed after recovery of normal bowel mobility.
Not known:	Gastrointestinal bleeding.
Hepatobiliary disorders	
Common:	Hepatic disorders: G1-2: 1.3%
Not known:	Transient elevations of liver function tests.
Skin and subcutaneous tissue disorders	
Very common:	Alopecia usually mild in nature: G1-2: 29.4%.
Common:	Skin reactions: G1-2: 5.7%.
Musculoskeletal and connective tissue disorders	
Common:	Arthralgia including jaw pain. Myalgia: G1-4: 7%; G3-4: 0.3%.
Renal and urinary disorders	
Common:	Dysuria: G1-2: 1.6%. Other genitourinary symptom: G1-2: 1.9%.
General disorders and administration site conditions	
Very common:	Fatigue/malaise: G1-4: 36.7%; G3-4: 8.5%. Fever: G1-4: 13.0%; G3-4: 12.1%.
Common:	Pain including pain at the tumour site: G1-4: 3.8%; G3-4: 0.6%. Chills: G1-2: 3.8%.
Investigations	
Very common:	Weight loss: G1-4: 25%; G3-4: 0.3%.
Common:	Weight gain: G1-2: 1.3%.

Adverse effects with NAVELBINE IV

In addition, some adverse effects have been observed with NAVELBINE IV from pre- and post-marketing experience which were not reported with NAVELBINE Oral. It cannot be ruled out that these effects may also be experienced with the use of NAVELBINE Oral as with other vinca alkaloids.

Table 5. Adverse effects reported of NAVELBINE IV

Infections and infestations	
Uncommon:	Septicaemia (very rarely fatal).
Immune system disorders	
Not known:	Systemic allergic reactions as anaphylaxis, anaphylactic shock or anaphylactoid type reactions.
Cardiac disorders	
Rare:	Ischemic cardiac disease (angina pectoris, myocardial infarction),
Very rare:	Pulmonary oedema, however a causal relationship has not been established, heart rhythm disorders.
Nervous system disorders	
Very common:	Weakness of lower extremities.
Uncommon	Severe paresthesias
Vascular disorders	
Uncommon:	Flushing and peripheral coldness.
Rare:	Severe hypotension, collapse
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Bronchospasm, as with other vinca alkaloids.
Rare:	Interstitial pneumopathy (in particular, in combination with mitomycin), sometimes fatal.
Unknown	Acute respiratory distress syndrome (ARDS)
Gastrointestinal disorders	
Rare:	Pancreatitis.
Skin and subcutaneous tissue disorders	
Rare:	Generalised cutaneous reactions.
Not known:	Palmar-plantar erythrodysesthesia syndrome.

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 Oral. No case of overdosage has been reported with NAVELBINE Oral, however 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. A close monitoring of hepatic function is recommended.

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 an 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.

Clinical trials

NAVELBINE IV

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 (30 mg/m²/week), vinorelbine (30 mg/m²/week), cisplatin (120 mg/m² days 1 and 29 then every 6 weeks), and vindesine (3 mg/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.

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.

In a randomised phase III study conducted to investigate efficacy in anthracycline-refractory advanced breast cancer, 115 patients received IV 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. IV 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. Summary of the efficacy results of trials of IV vinorelbine used in combination with other agents for the second-line treatment of patients with advanced breast cancer

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%

NAVELBINE Oral

Oral vinorelbine has been developed as a line extension of the IV dosage form. Hence, the primary objective of the clinical program was to demonstrate bioequivalence between the oral and intravenous formulations on the basis of pharmacokinetic studies. An oral dose of 80 mg/m² was demonstrated to correspond to 30 mg/m² of the IV formulation and 60 mg/m² orally to 25 mg/m² given by the IV route. Subsequent phase II studies were conducted to examine the efficacy and tolerance of oral vinorelbine.

Non-Small Cell Lung Cancer

One randomised phase II study (97 CA 205) with the recommended oral dose regimen was conducted, comparing oral and IV vinorelbine in patients with advanced or metastatic NSCLC who had not previously been treated with cytotoxic chemotherapy. The results are summarised in Table 7.

Table 7. Summary of the efficacy results of a randomised phase II study in NSCLC (97 CA 205)

Study I-CA 205	Oral vinorelbine	IV vinorelbine
No of subjects	77	38
Response rate (ITT population) (%)	11.7	10.5
Response rate (evaluable population) (%)	14.1	11.8
Median duration of response (months)	7.7	5.5
Median progression-free survival (months)	3.3	2.1
Median survival (months)	9.4	7.9

In a multicentre, phase II study of 56 patients in combination with cisplatin 100 mg/m² (day 1 q 4 weeks), the weekly administration of vinorelbine (IV vinorelbine 25 mg/m² day 1, oral vinorelbine 60 mg/m² days 8, 15 and 22) produced a reponse rate of 30% for all registered patients and 33% for evaluable patients in the first line treatment of unresectable, localised or metastatic NSCLC. Median progression-free survival and survival were 5.5 and 8.9 months, respectively.

Advanced breast cancer

As a single agent

Two non-comparative multi-centre phase II studies (96 CA 201 and 97 CA 206) of oral vinorelbine given weekly at a dose of 60 mg/m² for the first 3 weeks and then increased to 80 mg/m² as a single agent, were conducted in the first line treatment of advanced breast cancer. A total of 184 patients were enrolled.

The majority of patients had metastatic disease at study entry, visceral lesions and had received prior hormonotherapy. The proportion of patients having received prior neo/adjuvant chemotherapy was 49.2% (96 CA 201) and 26.5% (97 CA 206). No patient had received prior chemotherapy for advanced/metastatic disease.

The efficacy results are summarised in Table 8.

Table 8. Summary of the efficacy results for oral vinorelbine in monotherapy in advanced breast cancer (96 CA 201 and 97 CA 206)

	96 CA 201	97 CA 206
Number of patients		
entered	120	64
evaluable	108	58
Response rate		
ITT population	20.8	29.7
% [95% CI]	[14-29]	[18-41]
Evaluable patients	23.2	31.0
% [95% CI]	[16-32]	[19-43]
Median PFS (months) (ITT)	4.6	4.2
Median survival (months) (ITT)	19.3	23.9

ITT = Intent-to-treat; PFS = Progression free survival.

A response rate of 30% was reported in Study 97 CA 206 and 21% in Study 96 CA 201. The lower response rate observed in the latter study could be explained by the very poor prognosis features in the patients having received no prior adjuvant chemotherapy: 57% of patients had stage III_B – IV disease, 67% had a disease-free interval less than 2 years and 62% had at least 3 organs involved. In this subset of patients, the response rate was only 14%.

Median durations of progression-free survival and overall survival were consistent in the 2 studies: 4.6 and 4.2 months; and 19.3 and 23.9 months respectively.

A randomised phase II trial (CA221) assessed in parallel the efficacy and safety of oral vinorelbine at 60 mg/m² on days 1 and 8 every 3 weeks for the first cycle then increased to 80 mg/m² on days 1 and 8 every 3 weeks for subsequent cycles ; and IV vinorelbine at 25 mg/m² on days 1 and 8 every 3 weeks for the first cycle then increased to 30 mg/m² on days 1 and 8 every 3 weeks for subsequent cycles. The study was closed 2.5 years after its initiation due to low accrual (85 patients enrolled out of 230 planned). Premature closure of the study did not allow for the accurate assessment of the efficacy of oral vinorelbine. The following results were observed: response rate of 7% and disease control rate of 47.4% in the

oral arm; response rate of 22% and disease control rate of 51.9% in the IV arm. Median overall survival was similar in the 2 study arms: 9.4 months and 10.2 months respectively.

In combination

A randomised phase II study (CA 222) of the combination of oral vinorelbine with capecitabine versus a sequential regimen of oral vinorelbine and capecitabine versus the combination of docetaxel and capecitabine was carried out in 139 metastatic breast cancer patients previously treated with anthracyclines.

In combination with capecitabine, oral vinorelbine was given on days 1 and 8 of three-week cycles at 60 mg/m² for the first cycle and then at 80 mg/m². In the sequential regimen, patients received oral vinorelbine 60 then 80 mg/m²/week for a total of 3 three-week cycles and then 3 cycles of capecitabine. In the control arm, the standard regimen of docetaxel 75 mg/m² on day 1 and capecitabine every 3 weeks was used. In the 3 study arms, the dose of capecitabine was 2000 mg/m²/day administered from days 1 to 14 every 3 weeks.

Efficacy results in the 3 study arms are summarised in Table 9.

Table 9. Summary of the efficacy results of the randomised phase II study, CA 222

	Oral VRL 60/80 mg/m² on days 1 and 8 plus capecitabine 2000 mg/m²/day from Days 1 to 14 q3 wks.	Oral VRL 60/80 mg/m²/week for 3 cycles followed by capecitabine 2000 mg/m²/day from Days 1 to 14 for 3 cycles.	Docetaxel 75 mg/m² on day 1 plus capecitabine 2000 mg/m²/day from Days 1 to 14 q3 wks.
Number of patients treated	44	46	48
evaluable⁽¹⁾	41	41	41
Disease control rate⁽¹⁾			
ITT population	70.5	37.0	70.8
% [95% CI]	[54.8-83.2]	[23.2-52.5]	[55.9-83.0]
Evaluable patients	73.2	39	80.5
% [95% CI]	[57.1-85.8]	[24.2 - 55.5]	[65.1-91.2]
Response rate⁽¹⁾			
ITT population	31.8	8.7	35.4
% [95% CI]	[18.6-47.6]	[2.4-20.8]	[22.2-50.5]
Evaluable patients	34.1	7.3	39.0
% [95% CI]	[20.1-50.6]	[1.5 - 19.9]	[24.2-55.0]
Median PFS (ITT)⁽²⁾			
Months [95% CI]	7.2 [5.3-8.9]	3.4 [2.6-5.6]	8.9 [7.2-12.0]
Median TTF (ITT)⁽²⁾			
Months [95% CI]	5.6 [4.2 - 6.5]	3.0 [1.8 - 4.4]	4.3 [4.0 - 5.0]

(1) According to independent panel review (2) According to investigator's evaluation.

ITT = Intent-to-treat; PFS = Progression free survival; TTF = Time-to-treatment failure.

The two combination arms, oral vinorelbine plus capecitabine and docetaxel plus capecitabine, produced similar disease control rates (70.5% vs 70.8% in the ITT population),

similar response rates (31.8% vs 35.4%), similar progression-free survival (7.2 months vs 8.9 months) and similar time-to-treatment failure (5.6 months vs 4.3 months). In comparison, the sequential regimen of oral vinorelbine followed by capecitabine was inferior to the combination regimens for all the efficacy parameters considered.

Oral vinorelbine in combination with other cytotoxics was assessed in three phase I/II studies: with epirubicin (Study CA 205); docetaxel (CA 101); and paclitaxel (CA 102).

The efficacy results of these studies are summarised in Table 10.

Table 10. Summary of the efficacy results in the ITT population of studies CA 205, CA 101 and CA 102

	Study CA 205 IV/oral VRL + epirubicin	Study CA 101 IV/oral VRL + docetaxel	Study CA 102 oral VRL + paclitaxel
Number of patients	49	49	48
Complete response	2	1	-
Response rate (%)	51	49	33.3
[95% CI]	[36.3 - 65.6]	[34.4 - 63.7]	[20.4 - 48.4]
Disease control rate (%)	86	82	69
[95% CI]	[76 - 96]	[71 - 93]	[55 - 82]
Median duration of response (months)	7.7	9.4	NA*
[95% CI]	[6.9 - 12.1]	[5.1 - 12.4]	
Median PFS (months)	8.1	5.5	5.0
[95% CI]	[6.9 - 9.8]	[4.2 - 7.2]	[4.2 - 7.4]
Median survival (months)	19.9	33.1	28.0
[95% CI]	[15.3 - 25.3]	[21.1 - 53.0]	[22.4 - not reached]

* Not calculated due to too many censored patients.

The two regimens alternating oral and IV vinorelbine in combination with epirubicin or docetaxel gave similar response rates of approximately 50%. Median durations of overall survival tended to be longer for the taxane combinations than for the combination with epirubicin.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration, NAVELBINE is promptly absorbed and the T_{max} is reached within 1.5 to 3 hours with a blood concentration peak (C_{max}) of approximately 130 ng/mL after dosing at 80 mg/m². The absolute bioavailability is about 40% and simultaneous intake of a low fat standard meal does not modify the area under the concentration-time curve (AUC). The effect of a high fat meal on absorption has not been studied.

NAVELBINE Oral 60 and 80 mg/m² leads to a comparable AUC to that obtained from 25 and 30 mg/m² of the IV formulation respectively. Interindividual variability of the AUC is

similar after administration by both the IV and oral routes. There is a proportional increase between the AUC and dose.

Distribution

The mean pharmacokinetic parameters were evaluated in blood. After intravenous administration, the terminal half-life averaged 38 hours. Blood clearance was high, approached liver blood flow and averaged 0.72 L/hr/kg (range: 0.32 – 1.26 L/hr/kg), while steady state volume of distribution was large, averaged 21.2 L/kg (range: 7.5 – 39.7 L/kg), and indicated extensive tissue distribution.

Vinorelbine binds extensively to blood cells and especially platelets (70 – 80%), but less extensively (about 15%) to plasma proteins. There is a significant uptake of NAVELBINE in lungs, as assessed by pulmonary surgical biopsies showing up to a 300 fold greater concentration than in serum. NAVELBINE has not been detected in the central nervous system.

Metabolism

NAVELBINE is mostly metabolised by the CYP 3A4 isoform of the cytochrome P450. All the metabolites have been identified and none are active except 4-O-deacetylvinorelbine which is the main metabolite in blood. No sulfo- or glucurono- conjugates are observed.

Excretion

Renal elimination is low (<20% of the dose) and consists mostly of the parent compound. Biliary excretion is the predominant elimination route of both metabolites and unchanged NAVELBINE, which is the main recovered compound.

Renal impairment

The effect of renal dysfunction on NAVELBINE disposition has not been assessed, however, dose reduction, in the presence of renal insufficiency is not indicated with NAVELBINE due to its low renal elimination.

Hepatic impairment

Vinorelbine is cleared from the circulation primarily by the liver, and therefore elevated blood concentrations may be expected in patients with hepatic impairment. In a phase I pharmacokinetic study, 6 subjects with severe hepatic impairment were treated with 20 mg/m² intravenously. Blood concentrations were elevated compared to historical data from patients with normal hepatic function. Oral vinorelbine is contraindicated in patients with severe hepatic impairment. In studies in patients with mild and moderate hepatic impairment, the pharmacokinetics of orally administered vinorelbine were not modified after administration of: 60 mg/m² in patients with mild hepatic impairment (bilirubin <1.5 x ULN and ALT and/or AST between 1.5 and 2.5 x ULN) and 50 mg/m² in patients with moderate hepatic impairment (bilirubin between 1.5 and 3 x ULN, independent of ALT and AST levels). Haematological toxicity should be closely monitored.

Pharmacokinetics/pharmacodynamic relationships

A strong relationship was demonstrated between AUC and leucocyte or PMN decreases.

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 tumorigenic 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 Oral also contains the following excipients: ethanol, purified water, glycerol and macrogol 400. The capsule shell contains: gelatin, Anidrisorb 85/70, Phosal 53 MCT, medium-chain triglycerides, glycerol, edible ink red, titanium dioxide, iron oxide yellow or iron oxide red.

6.2 INCOMPATIBILITIES

Not applicable.

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) in the original container. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

PVC/PVDC/Al blister packs.

Pack size: 1 capsule

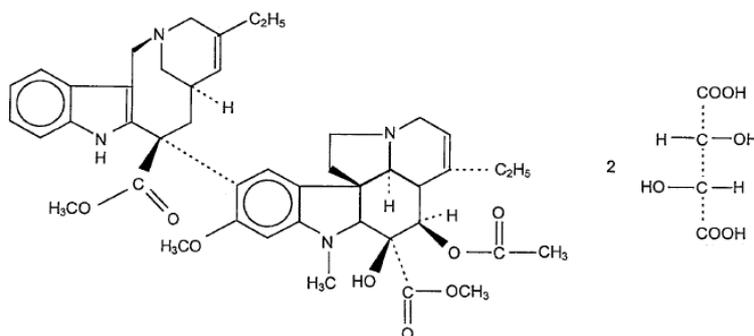
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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'-norvincaloblastine [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 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

8 SPONSOR

Pierre Fabre Australia Pty Limited
Level 7, 32 Walker St
North Sydney, NSW 2060
Australia

9 DATE OF FIRST APPROVAL

31 May 2005

10 DATE OF REVISION

12 November 2021

Summary table of changes

Section changed	Summary of new information
8	Sponsor address updated