

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DBL™ Vinorelbine Injection Concentrate

10mg/mL

Concentrate for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL™ Vinorelbine Injection Concentrate contains 10 mg vinorelbine tartrate equivalent to 10 mg vinorelbine per mL (present as 13.85 mg of vinorelbine tartrate).

3. PHARMACEUTICAL FORM

DBL™ Vinorelbine is a concentrate for injection. It is a clear colourless to pale yellow solution. The pH of DBL™ Vinorelbine Injection Concentrate is approximately 3.0 to 4.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DBL™ Vinorelbine Injection Concentrate 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

Dose

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

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

DBL™ Vinorelbine Injection Concentrate should be administered either by slow bolus over 6 to 10 minutes after dilution in 50mL of a normal saline solution or by a short infusion over 20 to 30 minutes, after dilution in 125mL of normal saline solution. Administration should always be followed by at least 250mL normal saline infusion to flush the vein.

Dose Adjustments

Dosage in patients with haematological toxicity

Neutrophil counts should be ≥ 1000 cells/mm³ prior to the administration of Vinorelbine Injection Concentrate. Adjustments in the dosage of DBL™ Vinorelbine Injection Concentrate 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 Vinorelbine (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 Vinorelbine Injection Concentrate.

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

22.5 mg/m² for neutrophils ≥ 1500 cells/mm³

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

Dosage in patients with hepatic insufficiency

DBL™ Vinorelbine Injection Concentrate should be administered with caution to patients with hepatic insufficiency. In patients who develop hyperbilirubinaemia during treatment with Vinorelbine Injection Concentrate, 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 Vinorelbine (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.

Special populations

Paediatric population

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.

Method of Administration

Administration Precautions

Caution - DBL™ Vinorelbine Injection Concentrate must be only administered intravenously through an infusion line. It is extremely important that the intravenous needle or catheter be properly positioned before any DBL™ Vinorelbine Injection Concentrate is injected. Leakage into surrounding tissue during intravenous administration of DBL™ Vinorelbine Injection Concentrate may cause considerable irritation, local tissue necrosis, and/or thrombophlebitis. If extravasation occurs, the injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein. Since there are no established guidelines for the treatment of extravasation injuries with Vinorelbine Injection Concentrate, institutional guidelines may be used.

As with other toxic compounds, caution should be exercised in handling and preparation of the solution of Vinorelbine Injection Concentrate. Skin reactions may occur with accidental exposure. The use of gloves is recommended. If the solution of DBL™ Vinorelbine Injection Concentrate 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 Vinorelbine Injection Concentrate, 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.

DBL™ Vinorelbine Injection Concentrate 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, DBL™ Vinorelbine Injection Concentrate should not be administered.

Preparation for administration

DBL™ Vinorelbine Injection Concentrate 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 DBL™ Vinorelbine Injection Concentrate must be followed with at least 250 mL of one of the solutions.

Syringe

The calculated dose of DBL™ Vinorelbine Injection Concentrate should be diluted to a concentration between 1.5 and 3.0 mg/mL. The following solutions may be used for dilution.

- 5% Dextrose Injection, USP

- 0.9% Sodium Chloride Injection, USP

IV Bag

The calculated dose of DBL™ Vinorelbine Injection Concentrate should be diluted to a concentration between 0.5 and 2 mg/mL. The following solutions may be used for dilution.

- 5% Dextrose Injection, USP
- 0.9% Sodium Chloride Injection, USP
- 0.45% Sodium Chloride Injection, USP
- 5% Dextrose and 0.45% Sodium Chloride Injection, USP
- Ringer's Injection, USP
- Lactated Ringer's Injection, USP

After diluting DBL™ Vinorelbine Injection Concentrate in normal saline or dextrose solution, the shelf life in the clear glass vials or in PVC perfusion bags is 24 hours at storage below 30° C.

DBL™ Vinorelbine Injection Concentrate should not be diluted in alkaline solutions due to the risk of precipitation.

DBL™ Vinorelbine Injection Concentrate should not be mixed with other agents.

DBL™ Vinorelbine Injection Concentrate is not absorbed to or affected by either PVC or clear neutral glass.

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

Diluted DBL™ Vinorelbine Injection Concentrate 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.

However, to reduce microbiological hazard, the diluted solution should preferably be used immediately and any residue discarded. If the diluted product cannot be used immediately or as soon as practical after preparation, store at 2-8° C for not more than 24 hours.

4.3 Contraindications

Known hypersensitivity to vinorelbine or other vinca alkaloids.

Neutrophil counts < 1000 cells/mm³, or severe infection due to neutropenia.

Severe hepatic insufficiency.

Pregnancy.

Lactation.

4.4 Special warnings and precautions for use

Vinorelbine Injection Concentrate should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.

Administration

Vinorelbine Injection Concentrate must only be administered by the intravenous route. Intrathecal administration of other vinca alkaloids has resulted in death. Improper administration of Vinorelbine Injection Concentrate may result in extravasation causing local tissue necrosis and/or thrombophlebitis (see section 4.2).

Myelosuppression

Patients treated with Vinorelbine Injection Concentrate 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 Vinorelbine Injection Concentrate is used as single agent or in combination, with neutrophil count recovery usually within 7 to 14 days after administration. Complete blood counts with differentials should be performed and results reviewed prior to administering each dose of Vinorelbine Injection Concentrate. Vinorelbine Injection Concentrate should not be administered to patients with neutrophil counts < 1000 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).

Vinorelbine Injection Concentrate 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).

Laboratory tests

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

General

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

Patients presenting with ischaemic cardiac disease should be carefully monitored (see section 4.8).

Acute shortness of breath and severe bronchospasm have been reported infrequently following the administration of Vinorelbine Injection Concentrate and other vinca alkaloids, most commonly when the vinca alkaloid was used in combination with mitomycin. These

adverse events may require treatment with supplemental oxygen, bronchodilators, and/or corticosteroids, particularly when there is a pre-existing pulmonary dysfunction.

Care must be taken to avoid contamination of the eye with concentrations of Vinorelbine Injection Concentrate used clinically. Severe irritation of the eye has been reported with accidental exposure to another vinca alkaloid, and even corneal ulceration if the drug is sprayed under pressure. If exposure occurs, the eye should immediately be thoroughly flushed with water.

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

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

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

Geriatric Use

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 population

Safety and effectiveness have not been established.

4.5 Interaction with other medicines and other forms of interaction

Acute pulmonary reactions have been reported with vinorelbine tartrate and other vinca alkaloids used in conjunction with mitomycin. Vinorelbine Injection Concentrate should be administered with caution in combination with mitomycin. Although the pharmacokinetics of vinorelbine are not influenced by the concurrent administration of cisplatin, the incidence of toxicities, specifically granulocytopenia, with the combination of Vinorelbine Injection Concentrate and cisplatin is significantly higher than with single-agent Vinorelbine Injection Concentrate.

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.

Based on the available limited information, it is possible that interaction may occur with other drugs which are metabolised via the cytochrome CYP3A4.

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.

Pregnancy

Category D

Vinorelbine tartrate 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 fetal effects in animals were lower than the human dose. There are no studies in pregnant women. If Vinorelbine Injection Concentrate 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 Vinorelbine Injection Concentrate.

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 Vinorelbine Injection Concentrate, it is recommended that nursing be discontinued in women who are receiving therapy with Vinorelbine Injection Concentrate.

4.7 Effects on ability to drive and use machinery

No data available

4.8 Undesirable effects

Haematological

Neutropenia is the major dose-limiting toxicity with vinorelbine tartrate. Neutropenia (Grade 3: 25.2%, Grade 4: 28.4%) is rapidly reversible (7 to 14 days) and non-cumulative. It is maximal between 5 and 10 days after administration, depending on whether Vinorelbine Injection Concentrate is used as single agent or in combination. Further treatment may be given after recovery of the neutrophil count. Anaemia (Grade 3 to 4: 8%) and thrombocytopenia (Grade 3 to 4: 2.3%) can also occur. Dose adjustments are required for haematologic toxicity and hepatic insufficiency (see section 4.2).

Neurological

Mild to moderate peripheral neuropathy manifested by paraesthesia and loss of deep tendon reflexes (Grade 3: 2.5%, Grade 4: 0.2%) 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 which rarely progresses to paralytic ileus (Grade 3: 2%, Grade 4: 0.6%). Treatment may be resumed after recovery of normal bowel mobility.

Gastrointestinal

Constipation (see above), mild to moderate nausea occurred in 25.5% of patients treated with vinorelbine tartrate. Severe nausea and vomiting (Grade 3: 2%, Grade 4: 0.3%) occurred less frequently. Due to the low incidence of severe nausea and vomiting with single-agent Vinorelbine Injection Concentrate, the use of serotonin antagonists is generally not required.

Stomatitis and diarrhoea, usually mild to moderate, may occur.

Pancreatitis has been reported very rarely.

Dermatological

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

Rarely vinorelbine tartrate may produce generalised cutaneous reactions.

Like other anticancer vinca alkaloids, Vinorelbine Injection Concentrate is a moderate vesicant.

Injection site reactions, including erythema, pain at injection site, and vein discoloration 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. In rare cases local tissue necrosis has been observed. Bolus injection followed by liberal flushing of the vein can limit this effect. Insertion of a central venous line may be necessary.

Hepatic

Transient elevations of liver enzymes were reported without clinical symptoms.

Respiratory

Shortness of breath was reported in 3% of patients. Vinorelbine tartrate, like other vinca alkaloids, may produce bronchospasm. Rare cases of interstitial pneumopathy have been reported, in particular in patients treated with vinorelbine tartrate in combination with mitomycin.

Cardiovascular

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. A few cases of

myocardial infarction, angina pectoris and/or transient ECG changes have been reported (see section 4.4).

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

Other

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

Rare cases of severe hyponatraemia have been reported.

Adverse Events Observed in Pivotal Phase III studies

	Total Vinorelbine %	Total Vinorelbine 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		1.0
Grade 3	2.0	2.9		1.5
All grades	25.5	26.9		5.9
- Nausea/ Vomiting				
Grade 4	0.3	1.4	1.0	2.9
Grade 3	2.0	18.4	24.0	0.0
All grades	31.3	68.1	72.4	24.9
Dermatological				
- Alopecia				
Grade 4	0.1	0.4	0.0	0.0
Grade 3	3.7	19.7	13.5	2.9
All grades	23.9	57.2	56.2	10.3
- Local phlebitis				
Grade 4	0.1	0.5	0.0	0.0
Grade 3	3.3	3.2	0.0	0.0
All grades	22.5	19.8	6.8	1.5
Cardiovascular				
- Cardiac events				
Grade 4	0.3	2.3		0.0
Grade 3	0.6	0.5		0.0
All grades	3.0	5.1		3.0
Others				
- Infection				
Grade 4	1.2	7.1		0.0
Grade 3	1.5	5.3		0.0
All grades	12.0	26.8		0.0

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

VDS = vindesine

CDDP = cisplatin

LV = Leucovorin

Reporting of suspected adverse reactions

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 Vinorelbine Injection Concentrate. The primary anticipated complications of overdosage would consist of bone marrow suppression and peripheral neurotoxicity. If overdosage occurs, general supportive measures together with appropriate blood transfusions and antibiotics should be instituted as deemed necessary by the 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

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 (2µM), including a blockade of cells at metaphase. Vincristine produced depolymerisation of axonal tubules at 5µM, but vinblastine and vinorelbine did not have this effect until concentrations of 30µM and 40µM 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

The demonstration of vinorelbine activity as a single agent in the treatment of advanced breast cancer is based on 8 phase II studies and one phase III study, totalling 577 patients. In the four trials where vinorelbine was used as first-line treatment, the overall response rate ranged from 41% to 60%. Of the total 283 evaluable patients, 128 had objective responses, ie response rate of 45.2% (CI95% 39.4% - 51%), duration of response 8.7 months. In the three phase II studies of vinorelbine administered weekly in second or third line treatment of advanced breast cancer, the response rate ranged from 19.6% to 30.3%. Based on an intention-to-treat analysis of evaluable patients in the two studies which used the recommended dose of 30 mg/m² weekly, the overall response rate was 24% and median duration 4.4 months. Results of the eighth phase II study are not presented here because of the different mode of administration used.

In a randomised phase III study conducted to investigate efficacy in anthracycline-refractory advanced breast cancer 115 patients received vinorelbine as a single agent versus 64 patients who received intravenous melphalan. The median dose, number of doses and duration of treatment for vinorelbine were 27.5 mg/m², 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 38 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 was also investigated in combination with other chemotherapy agents in advanced breast cancer. In a phase II study, a combination of vinorelbine plus doxorubicin

resulted in an overall response rate of 74% (66 objective responses out of 89 evaluable patients), with an overall median duration of response of 12 months and a median time to progression of 13.2 months. The median survival of patients attaining complete response had not yet been reached with a median follow up of 30 months. The median survival of patients attaining a partial response was 22.4 months. The overall median survival was 27.5 months.

In a phase II study of the combination of vinorelbine plus 5-fluorouracil, an overall response rate of 64% was found (40 out of 63 evaluable patients), with an overall median duration of response of 12.3 months, median time to progression of 12.7 months and an overall median survival of 23 months (28.1 months for responding patients).

Non-small cell lung cancer

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 (30mg/m²/week), vinorelbine (30 mg/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

Following intravenous administration of vinorelbine tartrate 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. The prolonged terminal phase is due to relatively slow efflux of vinorelbine from peripheral compartments. The terminal phase half-life averages 27.7 to 43.6 hours and the mean clearance ranges from 0.6 to 1.3 L/h/Kg.

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

Vinorelbine undergoes substantial hepatic elimination in humans, with large amounts recovered in faeces after intravenous administration to humans. One active metabolite, deacetylvinorelbine, has been detected but not quantified in human plasma. The effects of renal or hepatic dysfunction on the disposition of vinorelbine have not been assessed, but based on experience with other anticancer vinca alkaloids, dose adjustments are recommended for patients with impaired hepatic function (see section 4.2).

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.

Reproductive and developmental toxicity

See section 4.6.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

Nitrogen

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months from date of manufacture stored at 2° to 8°C (Refrigerate, do not freeze) protect from light.

24 hours reconstituted stored at 2° to 8°C (Refrigerate, do not freeze)

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

DBL™ Vinorelbine Injection Concentrate is a clear colourless to pale yellow solution in water for injections containing 10 mg vinorelbine per mL. DBL™ Vinorelbine Injection Concentrate is available in single-use, clear glass vials with black or grey elastomeric stoppers and green plastic caps, individually packaged in a single vial carton in the following vial sizes:

- 10 mg/1 mL Single-Use Vial
- 50 mg/5 mL Single-Use Vial

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

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

7 July 2005

10. DATE OF REVISION OF THE TEXT

20 February 2019

Summary table of changes

Section changed	Summary of new information
All	Reformat to MedSafe Data Sheet guidance