

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DBL™ Vinblastine Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DESCRIPTION

DBL™ Vinblastine Sulfate B.P. is the sulfate of an alkaloid, occurring in the **Vinca rosea Linn.**, (a common, flowering herb).

Vinblastine Injection is a sterile solution of DBL™ Vinblastine Sulfate B.P. in Sodium Chloride 0.9% Injection.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

The pH of the solution is 3.5 -5.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vinblastine is effective as a single agent, but its therapeutic effect is enhanced when used in combination with other antineoplastic drugs.

Vinblastine has been used in the treatment of Hodgkin's disease (Stages III and IV) in combination therapy (with adriamycin (doxorubicin), bleomycin and dacarbazine as ABVD) and in the treatment of advanced testicular carcinoma (with cisplatin and bleomycin).

Vinblastine has been used in the palliative treatment of lymphocytic lymphoma, histiocytic lymphoma, advanced stages of mycosis fungoides, Kaposi's sarcoma and Histiocytosis X.

Vinblastine may be used in the treatment of choriocarcinoma resistant to other chemotherapeutic agents; carcinoma of the breast, unresponsive to appropriate endocrine surgery and hormonal therapy.

One of the most effective single agents for treatment of Hodgkin's disease is vinblastine. A protocol substituting cyclophosphamide for nitrogen mustard and vinblastine for vincristine in MOPP [mechlorethamine hydrochloride (nitrogen mustard), vincristine sulfate, prednisone and procarbazine] is an alternative therapy for previously untreated patients with advanced Hodgkin's disease. Patients suffering relapse have also responded to combination therapy that included vinblastine.

Advanced testicular germ-cell cancers are sensitive to vinblastine alone but the administration of vinblastine concomitantly with other antineoplastic agents, produces better clinical results. Bleomycin effectiveness is enhanced when vinblastine is administered 6 to 8 hours prior to bleomycin administration; this schedule permits more cells to be arrested during metaphase, in which bleomycin is active.

4.2 Dose and method of administration

Dose

DBL™ Vinblastine Injection is for intravenous use only. In order to avoid the risk of extravasation it is extremely important that the needle be properly positioned in the vein before the product is injected.

It is recommended that Vinblastine Injection be administered ONCE EVERY 7 DAYS. Therapy is initiated in adults by the administration of a single intravenous dose of 3.7 mg/m² bsa (body surface area). Thereafter white blood cell counts should be made to determine the patient's sensitivity to vinblastine.

Recommended incremental approach to dosage at WEEKLY INTERVALS as follows:

	Adults mg/m ² bsa	Children mg/m ² bsa
First dose	3.7	2.5
Second dose	5.5	3.75
Third dose	7.4	5.0
Forth dose	9.25	6.25
Fifth dose	11.1	7.5

Dosage increase may be continued but must not exceed 18.5 mg/m² bsa for adults and 12.5 mg/m² bsa for children. Dosage should not be increased after the dose which reduces white cell count to approximately 3.0 x 10⁹/L (3000/mm³).

For most adult patients the dosage will be 5.5 to 7.4 mg/m² bsa. However, leukopenia can be produced at 3.7 mg/m² bsa; others may require 11.1 mg/m² bsa, and very rarely 18.5 mg/m² bsa.

A maintenance dosage is administered ONCE WEEKLY, one increment smaller than the dosage to produce the above degree of leukopenia. Hence, the patient is receiving the maximum dosage that does not cause leukopenia.

IT SHOULD BE EMPHASIZED THAT, EVEN THOUGH 7 DAYS HAVE ELAPSED, THE NEXT DOSE OF DBL™ VINBLASTINE INJECTION SHOULD NOT BE GIVEN UNTIL THE WHITE CELL COUNT HAS RETURNED TO AT LEAST $4.0 \times 10^9/L$ (4000/mm³). In some cases, oncolytic activity may be encountered before leukopenic effect. When this occurs, there is no need to increase the size of subsequent doses.

Maintenance therapy duration is dependent upon the disease being treated and the antineoplastic agent combination. Maintenance therapy for treatment of Hodgkin's disease is subject to varying opinions as to duration. Prolonged chemotherapy for maintaining remissions involves several risks, among which are life-threatening infectious diseases, sterility and possibly the appearance of other cancers through suppression of immune surveillance.

Method of Administration

DBL™ Vinblastine Injection is a sterile solution of vinblastine sulfate in sodium chloride 0.9% injection.

The calculated dose of the solution may be injected either directly into the vein or into the injection site of a running intravenous infusion. Intravenous administration of Vinblastine Injection may be completed in about one minute.

Care should be taken to avoid infiltration of subcutaneous tissues (see section 4.4).

DBL™ Vinblastine Injection may be further diluted with compatible solutions (0.9% saline or 5% glucose) for the purpose of I.V. infusion. However, dilution in large volumes of diluent (100-250 mL) or prolonged infusion, is not recommended, since this may cause irritation and increase the risk of extravasation. To avoid microbial contamination hazards infusion should be commenced as soon as practicable after preparation of the mixture. Infusion should be completed within 24 hours of preparation of the solution and any residue discarded.

Diluted solutions which are not clear or show evidence of particulate matter should be discarded.

Caution is advised when injecting vinblastine into extremities. If the circulation is impaired, the risk of thrombosis is increased.

Compatibility

DBL™ Vinblastine Injection has been found to be compatible when added to sodium chloride 0.9% injection and glucose 5% injection.

4.3 Contraindications

Vinblastine is contraindicated in patients who have experienced hypersensitivity reactions with this drug.

Vinblastine is contraindicated in patients who are leukopenic.

It should not be used in the presence of bacterial infection. Such infections should be brought under control with antiseptics or antibiotics before the initiation of therapy with vinblastine.

4.4 Special warnings and precautions for use

Warnings

Vinblastine must be used only by physicians experienced in cytotoxic chemotherapy.

This preparation is for intravenous use only.

Because of the possibility of fatal reactions, Vinblastine Injection must not be given intramuscularly, subcutaneously or intrathecally. The intrathecal administration of Vinblastine Injection has resulted in death.

As with other antineoplastic agents, Vinblastine Injection may cause a severe local reaction on extravasation. If leakage into the surrounding tissue should occur during intravenous administration of vinblastine, the injection should be discontinued immediately and any remaining portion of the dose should be introduced into another vein. Local injection of hyaluronidase with the application of heat has been used to disperse the drug in order to minimise discomfort and the possibility of tissue damage.

Caution is advised when injecting vinblastine into extremities. If the circulation is impaired, the risk of thrombosis is increased.

Liver disease may alter the elimination of vinblastine in the bile, markedly increasing toxicity to peripheral nerves and necessitating a dosage modification in affected patients.

Precautions

Patients should be carefully monitored for infection until white cell count has returned to normal levels if leukopaenia with less than 2.0×10^9 white blood cells per litre ($2000/\text{mm}^3$) occurs following a dose of Vinblastine Injection.

When cachexia or ulcerated areas of the skin surface are present, there may be more profound leukopaenic response to the drug; therefore its use should be avoided in older persons suffering from either of these conditions.

Leucocyte and platelet counts have sometimes fallen precipitously after moderate doses of Vinblastine Injection in patients with malignant-cell infiltration of the bone marrow. Further use of the drug in such patients is inadvisable.

The use of small amounts of Vinblastine Injection daily for long periods of time is not advised, since little or no added therapeutic effect has been demonstrated, even though the resulting total weekly dosage may be similar.

It is important to strictly adhere to the recommended dosage schedule.

Convulsions, severe and permanent central nervous system damage and even death have occurred when amounts of several times the recommended weekly dosage were given in 7 daily instalments for long periods.

Avoid contamination of the eye with Vinblastine Injection. If accidental contamination occurs, severe irritation (or corneal ulceration if delivered under pressure) may result. Wash the eye with water immediately and thoroughly.

A risk-benefit assessment should be considered when the following medical problems exist in patients who are to receive Vinblastine Injection: chicken pox (existing or recent exposure), herpes zoster, gout or a history of urate renal stones, impaired hepatic function and infection.

4.5 Interaction with other medicines and other forms of interaction

Caution should be exercised with the concomitant administration of Vinblastine Injection with bone marrow suppressant drugs such as azathioprine, interferon, chloramphenicol, amphotericin B, colchicine, flucytosine and zidovudine.

The simultaneous oral or intravenous administration of phenytoin and antineoplastic chemotherapy combinations that included Vinblastine Injection have been reported to have reduced blood levels of phenytoin and to have increased seizure activity. Dosage adjustment should be based on phenytoin blood level monitoring. The contribution of vinblastine to this interaction is not certain. The interaction may result from either reduced absorption of phenytoin or an increase in the rate of its metabolism and elimination.

Immunisation with live vaccines in patients being treated with Vinblastine Injection may result in a potentially life-threatening infection. The immune response of the body is suppressed by vinblastine. The effectiveness of the vaccine may be poor and generalised infection may occur in patients immunised with live vaccines. Live vaccines should not be administered to patients being treated with vinblastine.

The chemotherapy drug regimen of vinblastine, bleomycin and cisplatin appears to cause serious life-threatening cardiovascular toxicity. One report describes five patients under treatment for germ cell tumours who died from acute life-threatening vascular events (myocardial infarction, rectal infarction, cerebrovascular accident) following VBP therapy. This drug combination is very effective in the treatment of testicular carcinoma but its potential toxicity is serious.

There are several reports describing an increase in lung disease in patients treated with a combination of vinblastine and mitomycin. Diffuse lung damage characterised by interstitial infiltrates and pleural effusions resulting in respiratory distress and cough have been described after treatment with vinblastine. The potential hazards of combining vinblastine and mitomycin necessitate the avoidance of this combination.

4.6 Fertility, pregnancy and lactation

Fertility

No data available.

Pregnancy

Category D. This category includes drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Consult literature for further information.

Caution is necessary with the use of vinblastine during pregnancy. Animal studies suggest that teratogenic effects may occur. The drug should not be used in pregnant women unless the expected benefit outweighs the potential risk. Aspermia has been reported in man.

Lactation

Although very little information is available regarding excretion of anti-neoplastic agents in breast milk, breast-feeding is not recommended while vinblastine is being administered because of the risks to the infant.

4.7 Effects on ability to drive and use machinery

No data available.

4.8 Undesirable effects

Patients should be advised of the possibility of untoward symptoms before the use of this product.

The incidence of side effects with use of vinblastine appears to be dose related. In general most side effects do not persist longer than 24 hours. Neurologic effects are not common but can occur and may last for more than 24 hours. Leukopenia, the most common side effect, is usually the dose limiting factor.

Side effects reported have been:-

Haematological: Leukopenia, anaemia, thrombocytopenia.

Gastrointestinal: Nausea, vomiting, constipation, vesiculation of the mouth, adynamic ileus, diarrhoea, anorexia, abdominal pain, rectal bleeding, pharyngitis, haemorrhagic enterocolitis, bleeding from a chronic peptic ulcer.

Neurologic: Numbness, paraesthesiae, peripheral neuritis, mental depression, loss of deep tendon reflexes, headache, convulsions.

Miscellaneous: Malaise, weakness, dizziness, pain in tumour site, vesiculation of the skin, hypertension, bone pain, jaw pain, Raynaud's phenomenon, inappropriate secretion of antidiuretic hormone (high dose), hypersensitivity reactions.

Antiemetic drugs may be used to control nausea and vomiting.

Alopecia is common. The development of epilation is usually not total and in some cases hair regrows during the continuance of maintenance therapy.

Extravasation during intravenous injection may lead to cellulitis and phlebitis. If amount of extravasation is great, sloughing may occur.

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

Clinical Features

The symptoms of overdosage are likely to be an extension of vinblastine's pharmacological action. Possible symptoms of toxicity are those listed under adverse reactions.

The major effect of toxic doses of Vinblastine Injection will be myelosuppression and this may be life threatening.

Management

Symptomatic supportive measures should be instituted. Particular attention should be given to prevention and treatment of possible severe infections secondary to severe, persistent bone marrow depression. Specialist texts should be consulted.

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

Vinblastine is a cytotoxic drug that arrests cell growth at the metaphase. Its actions are more pronounced on the rapidly dividing cell than on the normal cell.

5.2 Pharmacokinetic properties

Distribution

Vinblastine is rapidly cleared from the blood and distributed into the body tissues. It crosses the blood-brain barrier poorly and does not appear in the CSF in therapeutic concentrations.

Biotransformation

Vinblastine is extensively metabolised by the liver. It is converted to desacetyl-vinblastine which is more active on a weight basis than the parent compound.

Elimination

Vinblastine is excreted slowly in urine and in faeces via the bile.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

Reproductive and developmental toxicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Sodium chloride
- Sodium hydroxide
- Sulfuric acid
- Water for injection

6.2 Incompatibilities

No data available.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Intact vials of Vinblastine Injection should be stored at 2-8°C. Protect from light.

6.5 Nature and contents of container

Vinblastine Injection is available in vials containing 10 mg DBL™ Vinblastine Sulfate B.P. per 10 mL of injection.

<u>Strength</u>	Volume	Pack	DBL Code	
1mg/mL	10mL	5's	7021C	
1mg/mL	10mL	1's	7021A	

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, 1140

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

13 Feb 1992

10. DATE OF REVISION OF THE TEXT

30 January 2019

Summary table of changes

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