

AUSTRALIAN PRODUCT INFORMATION – DBL™ VINBLASTINE INJECTION (Vinblastine sulfate)

1. NAME OF THE MEDICINE

Vinblastine sulfate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

3. PHARMACEUTICAL FORM

Solution for injection.

The pH of the solution is 3.5 to 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; and carcinoma of the breast, unresponsive to appropriate endocrine surgery and hormonal therapy.

One of the most effective single agents for the 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

Dosage

DBL Vinblastine Injection is for intravenous use only. Fatal if given by any other route. Vinblastine should not be given intramuscularly, subcutaneously or intrathecally. 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 infused.

It is recommended that DBL 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.

The recommended incremental approach to dosage at WEEKLY INTERVALS is 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
Fourth 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 x 10⁹/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 the 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 infused via a flexible plastic container either directly into the vein or into the injection site of a running intravenous infusion.

Care should be taken to avoid infiltration of subcutaneous tissues (see 4.4 Special warnings and Precautions for Use).

DBL Vinblastine Injection may be further diluted with compatible solutions (0.9% saline or 5% glucose) for the purpose of IV infusion. However, dilution in large volumes of diluent (100 to 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 intravenously administering vinblastine into extremities. If the circulation is impaired, the risk of thrombosis is increased.

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

Compatibilities

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 medicine.

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. Fatal if given by any other route.

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 infusion 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 medicine in order to minimise discomfort and the possibility of tissue damage.

Caution is advised when infusing 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 leukopenia 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 leukopenic response to the medicine; 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 medicine 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 infection.

Use in hepatic impairment

A risk-benefit assessment should be considered in patients with a history of impaired hepatic function.

Use in renal impairment

A risk-benefit assessment should be considered in patients with a history of urate renal stones.

Use in the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Caution should be exercised with the concomitant administration of DBL 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 DBL 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 DBL 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 medicine regimen of vinblastine, bleomycin and cisplatin (VBP) 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

Effects on fertility

Aspermia has been reported in man.

Use in pregnancy – Pregnancy Category D

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

Use in 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 machines

Effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, adverse effects of vinblastine sulfate (with unknown frequency) may include dizziness and motor dysfunction which could affect the ability to drive or use machines. See Section 4.8 Adverse effects (undesirable effects). Patients should refrain from driving or using machines until they know that the medicinal product does not negatively affect these abilities.

4.8 Adverse effects (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 the amount of extravasation is great, sloughing may occur.

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

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 section 4.8 Adverse effects (undesirable effects).

The major effect of toxic doses of DBL 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 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

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.

Clinical trials

No data available.

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.

Metabolism

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.

Excretion

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride

Water for injections

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

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

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

6.5 Nature and contents of container

DBL Vinblastine Injection is available in vials containing 10 mg vinblastine sulfate per 10 mL of injection.

Strength	Pack	DBL Code	ARTG
10 mg/10 mL	5's	7021C	AUST R 16309
10 mg/10 mL	1's	7021A	AUST R 16309

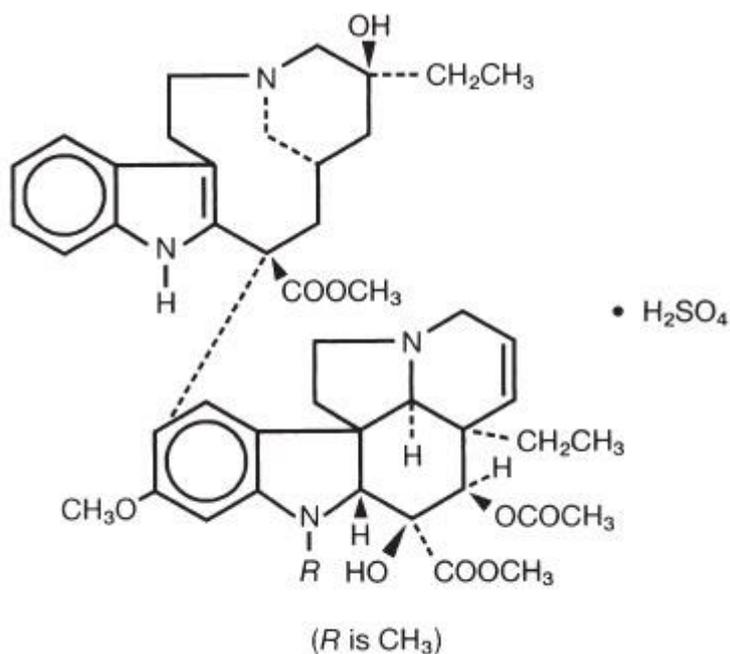
Not all pack sizes may be marketed.

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

Chemical structure



C₄₆H₅₈N₄O₉·H₂SO₄

M.W. 909.06

Vinblastine sulfate is the sulfate of an alkaloid, occurring in the *Vinca rosea* Linn., (a common, flowering herb). Its molecular formula is C₄₆H₅₈N₄O₉, H₂SO₄ and it has a molecular weight of 909.1.

CAS number

143-67-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

Date of TGA approval: 21 June 1994

10. DATE OF REVISION

27 August 2021

™ = Trademark

Summary Table of Changes

Section changed	Summary of new information
4.2	Update to include further warning that vinblastine is fatal if given by other routes and not intravenously. Update to remove reference to injection administration and including use of flexible plastic containers. Update of warning against syringe use for administration and preparation.
4.4	Update to include further warning that vinblastine is fatal if given by other routes and not intravenously. Removal of injecting wording and inclusion of infusing wording in line with update to Section 4.2.
4.7	Update to include adverse effects that may affect driving.