

DBL™ Vinblastine Injection

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/m² bsa	Children mg/m² 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.

FOR INTRAVENOUS USE ONLY. FATAL IF GIVEN BY OTHER ROUTES (see Section 4.4 Special warnings and precautions for use).

In case of mistaken administration by intrathecal route, see Section 4.4 Special warnings and precautions for use.

Care should be taken to avoid infiltration of subcutaneous tissues (see Section 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 DBL 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. Cytotoxic preparations should not be handled by pregnant staff.

This preparation is for intravenous use only. Fatal if given by any other route.

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

After inadvertent intrathecal administration of vinca alkaloids, immediate neurosurgical intervention is required in order to prevent ascending paralysis leading to death. In a very small number of patients, life-threatening paralysis and subsequent death was averted but resulted in devastating neurological sequelae, with limited recovery afterwards.

Based on the published management of survival cases involving the related vinca alkaloid vincristine sulfate, if vinblastine sulfate is mistakenly given by the intrathecal route, the following treatment should be initiated immediately after the injection:

1. Removal of as much cerebrospinal fluid (CSF) as is safely possible through the lumbar access.
2. Insertion of an epidural catheter into the subarachnoid space via the intervertebral space above initial lumbar access and CSF irrigation with lactated Ringer's solution. Fresh frozen plasma should be requested and, when available, 25 mL should be added to every 1 litre of lactated Ringer's solution.
3. Insertion of an intraventricular drain or catheter by a neurosurgeon and continuation of CSF irrigation with fluid removal through the lumbar access connected to a closed drainage system. Lactated Ringer's solution should be given by continuous infusion at 150 mL/hour, or at a rate of 75 mL/hour when fresh frozen plasma has been added as above.

The rate of infusion should be adjusted to maintain a spinal fluid protein level of 150 mg/dL.

In addition folinic acid, glutamic acid, and pyridoxine have also been used, but their roles in the reduction of neurotoxicity are unclear.

As with other antineoplastic agents, DBL 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. Cases of phlebitis, cellulitis and skin necrosis have been reported.

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

Amenorrhoea has occurred in some patients treated with vinblastine sulfate in combination with other drugs. Recovery of menses was frequent.

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

The dose-limiting factor is myelosuppression. In general, the larger the dose employed, the more profound and longer lasting the leukopenia will be. The fact that the granulocyte count

returns to normal levels after drug induced leukopenia is an indication that the granulocyte-producing mechanism is not permanently depressed.

Following therapy with vinblastine sulfate, the nadir in the granulocyte count may be expected to occur five to ten days after the last day of drug administration. Recovery of the granulocyte count is fairly rapid thereafter and is usually complete within another seven to fourteen days. If granulocytopenia with less than 1,000 granulocytes/mm³ occurs following a dose of vinblastine sulfate, the patient should be watched carefully for evidence of infection until the granulocyte count has returned to a safe level. Any infection must be brought under control immediately.

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/mm³) occurs following a dose of DBL 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.

Although the thrombocyte count is not usually significantly lowered by therapy with vinblastine sulfate, patients whose bone marrow has been recently impaired by prior therapy with radiation or with other oncolytic drugs may show thrombocytopenia (less than 150,000 platelets/mm³). When other chemotherapy or radiation has not been employed previously, thrombocyte reduction below the level of 150,000/mm³ is rarely encountered, even when vinblastine sulfate may be causing significant granulocytopenia. Rapid recovery from thrombocytopenia within a few days is the rule.

The effect of vinblastine sulfate upon the red blood cell count and haemoglobin is usually insignificant when other treatment does not complicate the picture.

Leucocyte and platelet counts have sometimes fallen precipitously after moderate doses of DBL 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 DBL Vinblastine Injection daily for long periods of time is not advised, since little or no added therapeutic effect has been demonstrated and side effects are increased, 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 DBL 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 DBL 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

When chemotherapy is being given in conjunction with radiation therapy through portals which include the liver, the use of vinblastine sulfate should be delayed until radiation therapy has been completed.

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. Although the contribution of the vinca alkaloids has not been established, dosage adjustment of phenytoin, based on serial blood level monitoring, may need to be made when it is used in combination with vinblastine sulfate. 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.

There have been reports of a decline in glomerular filtration rate which may be reversible, nephrotoxicity, pulmonary toxicity, peripheral sensory neuropathy, neurotoxicity, ototoxicity, azoospermia, irreversible high frequency hearing loss, Raynaud's phenomenon with digital ischaemia and gangrene, hypertension, and other vascular events, following co-administration of vinblastine sulfate, bleomycin and cisplatin (VBP). VBP therapy 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.

Vinblastine sulfate used as part of a combination regimen with mitomycin may result in fatal acute respiratory distress or failure. There are several reports describing an increase in lung disease such as pulmonary infiltration or pulmonary oedema 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.

Dyspnoea and severe bronchospasm have been reported following the administration of the vinca alkaloids. These reactions have been encountered most frequently when the vinca alkaloid was used in combination with mitomycin-C and may be serious when there is pre-existing pulmonary dysfunction. The onset may be within minutes, or several hours after the vinca is injected, and may occur up to 2 weeks following a dose of mitomycin. Progressive dyspnoea, requiring chronic therapy, may occur. Vinblastine sulfate should not be readministered.

Cases of respiratory distress with interstitial pulmonary infiltrates have been reported in patients given a regimen comprising vinblastine, mitomycin, with or without progesterone (MVP or MV).

Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP 3A subfamily, or in patients with hepatic dysfunction. Concurrent administration of vinblastine sulfate with an inhibitor of this metabolic pathway may cause an earlier onset and/or an increased severity of side effects.

Particular caution is warranted when vinblastine sulfate is used in combination with other agents known to be ototoxic, such as the platinum-containing oncolytics.

Co-administration of cisplatin has been reported to cause higher plasma concentrations of vinblastine and severity of neutropenia may be altered when given in conjunction with cisplatin.

Erythromycin may increase the toxicity of vinblastine which may cause increased severity of neutropenia, myalgia and constipation.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential should be advised to avoid becoming pregnant while receiving vinblastine sulfate. Due to the potential for genotoxicity, teratogenicity, and embryo toxicity, female patients of reproductive potential are advised to use highly effective contraception during treatment and for at least 7 months following last dose of vinblastine sulfate.

Due to the potential for genotoxicity, male patients with female partners of reproductive potential are advised to use highly effective contraception during treatment and for at least 4 months following the last dose of vinblastine sulfate.

Effects on fertility

Based on clinical reports, male and female fertility may be compromised. Aspermia has been reported in men. It is recommended to discuss fertility preservation with men and women prior to treatment.

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.

If vinblastine sulfate is used during pregnancy or if the patient becomes pregnant while receiving this drug, she should be informed of the potential hazard to the foetus.

Use in lactation

Very little information is available regarding excretion of anti-neoplastic agents in breast milk. It is not known whether vinblastine sulfate is excreted in human milk. Because of the potential for serious adverse reactions due to vinblastine sulfate in nursing infants, the mother should be advised not to breast-feed while on vinblastine sulfate therapy and for 1 week following last dose of treatment or to discontinue treatment, taking into account the importance of the drug to the mother.

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:

Blood and lymphatic system disorders: Leukopenia, anaemia, thrombocytopenia, neutropenia.

Endocrine disorders: Inappropriate secretion of antidiuretic hormone (high dose).

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

Nervous system disorders: Numbness, paraesthesia, peripheral neuritis, mental depression, loss of deep tendon reflexes, headache, convulsions, cerebrovascular accident^a, neurotoxicity.

Ear and labyrinth disorders: VIIIth nerve injury^b, ototoxicity.

Cardiac disorders: Myocardial infarction^a, hypertension.

Reproductive system and breast disorders: Aspermia.

Miscellaneous: Malaise, weakness, dizziness, pain in tumour site, vesiculation of the skin, bone pain, jaw pain, Raynaud's phenomenon, 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.

^a In combination chemotherapy with vinblastine sulfate, bleomycin and cisplatin.

^b Manifestations include partial or total deafness, which may be temporary or permanent, and difficulties with balance, including dizziness, nystagmus and vertigo.

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) in an enhanced intensity. Any dose that results in elimination of platelets and neutrophils from blood and marrow and their precursors from marrow is life-threatening.

The major effect of toxic doses of DBL Vinblastine Injection will be on granulocytopenia, including signs of myelosuppression and this may be life-threatening.

In addition, neurotoxicity may be observed.

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.

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
Sodium hydroxide
Sulphuric acid
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

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
10 mg/10 mL	5's
10 mg/10 mL	1's

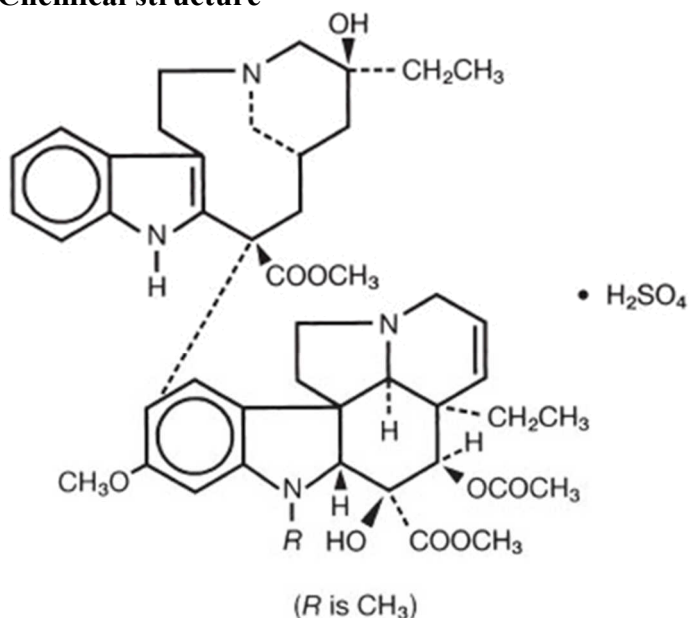
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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. NAME AND ADDRESS OF MANUFACTURER

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