DBL® Vinblastine Injection

1.0 NAME OF THE MEDICINE
Vinblastine sulfate

2.0 DESCRIPTION
Vinblastine sulfate is the sulfate of an alkaloid, occurring in the **Vinca rosea Linn.**, (a common, flowering herb). Its molecular formula is $C_{46}H_{58}N_4O_9$, H_2SO_4 and it has a molecular weight of 909.1.

3.0 PHARMACEUTICAL FORM
DBL® Vinblastine Injection is a sterile solution of vinblastine sulfate in sodium chloride 0.9% injection. The pH of the solution is 3.5 to 5.0.

4.0 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 Dosage 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/m^2 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/m^2 bsa for adults and 12.5 mg/m^2 bsa for children. Dosage should not be increased after the dose which reduces white cell count to approximately 3.0 x 10^9/L (3,000/mm^3).

For most adult patients the dosage will be 5.5 to 7.4 mg/m^2 bsa. However, leukopenia can be produced at 3.7 mg/m^2 bsa; others may require 11.1 mg/m^2 bsa, and very rarely 18.5 mg/m^2 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 10^9/L (4,000/mm^3). 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. Intravenous administration of DBL® Vinblastine Injection may be completed in about one minute.

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 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.

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

DBL® Vinblastine Injection is for intravenous use only. DBL® Vinblastine Injection must be used only by physicians experienced in cytotoxic chemotherapy.

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.

The following treatment successfully arrested progressive paralysis in a single patient mistakenly given the related vincristine sulfate, intrathecally. This treatment should be initiated immediately:

1. Removal of as much CSF as is safely possible through the lumbar access.

2. Flushing with Lactated Ringer's solution by continuous infusion at 150 mL/h, through a catheter in a cerebral lateral ventricle and removed through lumbar access, until fresh plasma became available.

3. Fresh frozen plasma, 25 mL, diluted with 1 litre of Lactated Ringer's was then infused similarly at 75 mL/h. The rate of infusion should be adjusted to maintain a spinal fluid protein level of 150 mg/dL.

4. Glutamic acid, 10 g, was given IV over 24 hours, followed by 500 mg tds by mouth for 1 month. Glutamic acid may not be essential.

Vinblastine SHOULD NOT BE GIVEN intramuscularly, subcutaneously or intrathecally.

Syringes containing this product should be over labelled with the intrathecal warning label provided - **'FOR INTRAVENOUS USE ONLY. FATAL IF GIVEN BY OTHER ROUTES'**.

As with other antineoplastic agents, vinblastine may cause a severe local reaction on extravasation. If leakage into the surrounding tissue should occur during intravenous administration of DBL® Vinblastine Injection, 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. Cases of phlebitis and cellulitis have been reported.

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.

The dose-limiting factor is myelosuppression. In general, the larger the dose employed, the more profound and longer lasting the leucopenia will be. The fact that the granulocyte count returns to normal levels after drug-induced leucopenia 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/mm^3 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 the white cell count has returned to normal levels if leucopenia with less than 2,000 white blood cells per mm^3 occurs following a dose of vinblastine sulfate.

When cachexia or ulcerated areas of the skin are present, a more profound granulocytopenic response may be produced by vinblastine. 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 DBL® Vinblastine Injection, 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/mm^3). When other chemotherapy or radiation has not been employed previously, thrombocyte reduction below the level of 150,000/mm^3 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.

In patients with malignant-cell infiltration of the bone marrow, the granulocyte and platelet counts have sometimes fallen drastically after moderate doses of vinblastine sulfate. Further use of the drug in such patients is inadvisable.

Breaks and aberrations were not observed on chromosome analysis of marrow cells from patients treated with DBL® Vinblastine Injection although chromosomal changes have been noted in some hamster lung cell *in vitro* tests.

Granulocytes and platelet counts have sometimes fallen precipitously after moderate doses of vinblastine sulfate in patients with malignant cell infiltration of the bone marrow. Further use of the drug in such patients is inadvisable.

Avoid contamination of the eye with vinblastine sulfate solution for injection. If accidental contamination occurs, severe irritation or corneal ulceration may result. The affected eye should be thoroughly irrigated with water immediately.

DBL® Vinblastine Injection contains sodium
DBL® Vinblastine Injection contains 35.42 mg sodium in each vial, equivalent to 1.77% of the WHO maximum recommended daily intake (RDI) of 2 g sodium for an adult.

4.5 Interactions with Other Medicinal Products and Other Forms of Interaction

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

Vinblastine used as part of a combination regimen with mitomycin may result in fatal acute respiratory distress or failure and there have been cases of pulmonary infiltration or pulmonary oedema reported.

Cases of respiratory distress with interstitial pulmonary infiltrates have been reported in patients given a regimen comprising vinblastine, mitomycin, with or without progesterone (MVP). Acute shortness of breath 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. DBL® Vinblastine Injection should not be re-administered.

The simultaneous administration of phenytoin and antineoplastic chemotherapy combinations that included vinblastine sulfate have been reported to reduce blood levels of the anticonvulsant and to increase 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.

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.

Following combined treatment with vinblastine, bleomycin and cisplatin, 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 ischemia and gangrene, hypertension and other vascular events (such as myocardial infarction and cerebrovascular accident).

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

Serum levels of anticonvulsants may be reduced by cytotoxic drug regimes, which include vinblastine.

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

There is no currently available evidence to indicate that vinblastine sulfate itself has been carcinogenic in humans, although some patients have developed leukaemia following radiation therapy and the administration of vinblastine sulfate in combination with alkylating agents.

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.

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 6 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 3 months following the last dose of vinblastine sulfate.

Pregnancy

Although information on the use of vinblastine during pregnancy is limited, the drug may cause foetal toxicity when administered to pregnant women. The drug causes resorption of foetuses in animals and produces gross foetal abnormalities in surviving offspring. There are no adequate and controlled studies to date using vinblastine in pregnant women, and the drug should be used during pregnancy only in life-threatening situations or severe disease for which safer drugs cannot be used or are ineffective.

If vinblastine is administered during pregnancy or the patient becomes pregnant while receiving the drug, the patient should be informed of the potential hazard to the foetus.

Fertility

The effect of vinblastine on fertility in humans is not fully known.

Based on clinical reports, male and female fertility may be compromised. Aspermia has been reported in men. Sperm abnormalities have been noticed in mice.

Additional studies in mice demonstrated no reduction in fertility in males. It is recommended to discuss fertility preservation with men and women prior to treatment.

Breast-feeding

It is not known whether vinblastine is excreted in human milk. Because of the potential for serious adverse reactions due to vinblastine in nursing infants, the mother should be advised not to breast-feed during the entire vinblastine sulfate therapy and for 1 week following last dose of treatment. Alternatively, a decision should be made whether to discontinue treatment with vinblastine sulfate, 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)

The use of small amounts of vinblastine daily for long periods is not advisable, even though the resulting total dosage may be similar to the recommended dosage. Little or no therapeutic advantage has been demonstrated when such regimens have been used and side-effects are increased.

The incidence of side effects with vinblastine sulfate appears to be dose related and most do not persist longer than 24 hours. Neurological effects are uncommon but can occur and may last longer than 24 hours.

The frequency grouping is defined using the following convention: Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations	
Not known	Pharyngitis
Neoplasms benign, malignant and unspecified (incl. cysts and polys)	
Not known	Tumour pain
Blood and lymphatic system disorders	
Not known	Neutropenia, Leucopenia[a], Thrombocytopenia, Anaemia
Endocrine disorders	
Not known	Inappropriate anti-diuretic hormone secretion[b]
Metabolism and nutrition disorders	
Not known	Anorexia
Psychiatric disorders	
Not known	Depression
Nervous system disorders	
Not known	Cerebrovascular accident[c], Convulsions, Numbness, Neuropathy peripheral, Loss of deep tendon reflexes, Paraesthesia, Headache, Dizziness
Ear and labyrinth disorders	
Not known	VIII[th] nerve injury[d]
Cardiac disorders	
Not known	Myocardial infarction[c]
Vascular disorders	
Not known	Hypertension, Raynaud's phenomenon[e]
Respiratory, thoracic and mediastinal disorders	
Not known	Dyspnoea[f], Acute respiratory distress[f]
Gastrointestinal disorders	
Not known	Haemorrhagic enterocolitis, Rectal bleeding, Peptic ulcer haemorrhage, Ileus, Nausea[g], Vomiting[g], Constipation, Oral mucosal blistering, Diarrhoea, Abdominal pain, Stomatitis
Skin and subcutaneous tissue disorders	
Not known	Blister, Alopecia[h]
Musculoskeletal and connective tissue disorders	
Not known	Myalgia, Bone pain, Jaw pain
Reproductive system and breast disorders	
Not known	Aspermia
General disorders and administration site conditions	
Not known	Injection site phlebitis, Injection site cellulitis (and in extreme cases skin exfoliation), Extravasation, Malaise, Asthenia

[a] Leucopenia is the most common side effect and dose limiting factor.

[b] Syndrome of inappropriate ADH secretion has been reported with higher than recommended doses.

[c] In combination chemotherapy with vinblastine sulfate, bleomycin and cisplatin.

[d] Treatment with vinca alkaloids has resulted rarely in both vestibular and auditory damage to the eighth cranial nerve. Manifestations include partial or total deafness, which may be temporary or permanent, and difficulties with balance including dizziness, nystagmus, and vertigo. Particular caution is warranted when vinblastine sulfate is used in combination with other agents known to be ototoxic, such as the platinum-containing oncolytics.

[e] Raynaud's phenomenon has occurred when patients are being treated with vinblastine in combination with bleomycin and cisplatin for testicular cancer.

[f] Reported when vinblastine is given in combinations with mitomycin (see section **4.5 Interactions with Other Medicinal Products and Other Forms of Interaction**).

[g] Antiemetics may be used to control nausea and vomiting.

[h] Usually not total and in some cases the hair regrows during maintenance therapy.

4.9 Overdosage

Side effects following the use of vinblastine are dose related. Therefore, following administration of more than the recommended dose, patients can be expected to experience these effects in an exaggerated fashion. 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 excessive doses of DBL® Vinblastine Injection will be on granulocytopoiesis, and this may be life-threatening.

In addition, neurotoxicity similar to that seen with vincristine sulfate may be observed.

Treatment: Supportive care should include: (1) prevention of the side effects that result from the syndrome of inappropriate secretion of antidiuretic hormone. This includes restriction of fluid intake and perhaps the use of a diuretic acting on the loop of Henle and distal tubule function; (2) administration of an anticonvulsant; (3) prevention and treatment of ileus; (4) monitoring the patient's cardiovascular system; and (5) daily blood counts for guidance in transfusion requirement and assessing the risk of infection.

There is no specific antidote. The use of folinic acid in addition to the other supportive measures recommended may be considered, although, unlike vincristine sulfate, studies have not been conducted to confirm its protective action.

There is no information regarding the effectiveness of dialysis nor of cholestyramine for the treatment of overdose.

Vinblastine sulfate in the dry state is irregularly and unpredictably absorbed from the gastro-intestinal tract following oral administration. Absorption of the solution has not been studied. If vinblastine sulfate is swallowed, activated charcoal in a water slurry may be given by mouth along with a cathartic. The use of cholestyramine in this situation has not been reported.

5.0 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.

6.0 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium Chloride
Water for injections

6.2 Compatibilities

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

6.3 Incompatibilities

Vinblastine sulfate is incompatible with furosemide, when injected sequentially into Y-site with no flush between or when mixed in syringe. Immediate precipitation results.

6.4 Presentation and Storage Conditions

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

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

7.0 MANUFACTURER

Hospira Australia Pty Ltd.
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Victoria, 3170,
Australia

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