

PRODUCT MONOGRAPH

PrVinblastine Sulfate Injection

1 mg/mL

Sterile Solution

Pfizer Standard

Antineoplastic Agent

Pfizer Canada ULC
17300 Trans-Canada Highway
Kirkland, Québec
H9J 2M5

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CAUTION

VINBLASTINE SULFATE IS A POTENT DRUG AND SHOULD BE USED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS. BLOOD COUNTS SHOULD BE TAKEN ONCE OR TWICE WEEKLY. DISCONTINUE OR REDUCE THE DOSAGE UPON EVIDENCE OF ABNORMAL DEPRESSION OF THE BONE MARROW. VINBLASTINE SULFATE INJECTION IS FOR INTRAVENOUS USE ONLY. IT IS FATAL IF GIVEN BY OTHER ROUTES.

ACTIONS AND CLINICAL PHARMACOLOGY

Tissue culture studies indicate that vinblastine is a selective mitotic inhibitor of certain malignant cells and as such appears to be different from other recognized antineoplastic drugs.

There is evidence that vinblastine interferes with cell metabolism and the entrance of glutamic acid into the citric acid cycle and to urea. There is also evidence that the anti-tumour effect of vinblastine may possibly be due to its effect on cell energy mechanisms and a decreased adenosine diphosphate production resulting from retarded nucleotide production. It has been suggested that the therapeutic ratio may depend on the greater energy needs of cancer cells along with their decreased efficiency in generating energy because of their reliance on the glycolytic pathway. These energy related actions for vinblastine have been brought forward because although it has been demonstrated that vinblastine has a stathmokinetic effect and produces various atypical mitotic figures in treated cells it has been observed clinically and experimentally that these cytological changes may occur in the absence of oncolytic effects.

It has also been demonstrated *in vitro* that vinblastine can prevent the invasion of normal tissue by malignant cells, thus preventing the spread of malignancy. The relationship of vinblastine to amino acid metabolism has been shown by a reversal of the anti-tumor effect of vinblastine by glutamic acid or tryptophan. As well, aspartic and glutamic acids had protected mice from lethal doses of vinblastine, although aspartic acid was relatively ineffective in reversing the anti-tumor effect of vinblastine.

Vinblastine has been shown in clinical practice to provide palliative treatment for a variety of malignant neoplastic diseases and in susceptible tumors produced a temporary reduction in the size of some tumors. Its use has relieved pain and other symptoms associated with neoplasm and permitted some patients to regain appetite and weight. Remission periods have varied from patient to patient.

Leukopenia is an expected effect of vinblastine and the leukocyte count is an important guide to vinblastine therapy. In general, the larger the dose, the longer lasting and more profound the leukopenia. However, the white cell producing mechanism is not permanently depressed by vinblastine, as it returns to normal on discontinuing treatment. Normally, when the white cells have essentially disappeared from the peripheral blood, the white count would have returned to normal. The nadir in white blood cell count usually occurs 5 - 10 days after the last treatment with vinblastine. Recovery is usually quite rapid and complete within another 7 - 14 days. If small doses are employed for maintenance therapy, leukopenia may not be clinically significant.

The thrombocyte count is not usually significantly reduced by vinblastine therapy; however, in patients whose bone marrow has been recently impaired by radiation therapy or other anti-neoplastic agents, thrombocytopenia may develop (less than 200,000 platelets per mm³). Thrombocyte values below 200,000 per mm³ are rarely encountered when other chemotherapeutic agents or radiation have not previously been used, even though significant leukopenia may be present. If thrombocytopenia does occur, it usually reverses within a few days after termination of treatment.

Vinblastine generally has an insignificant effect on red cell count and hemoglobin. However, patients with a malignant disease may have anemia even in the absence of antineoplastic therapy.

INDICATIONS AND CLINICAL USES

Vinblastine Sulfate is indicated in the palliative treatment of the following neoplastic diseases:

1. Frequently Responsive Malignancies

- Generalized Hodgkin's disease (Stages III and IV, Ann Arbor modification of Rye)
- Lymphocytic lymphoma (modular and diffuse, poorly and well differentiated)
- Histocytic lymphoma
- Mycosis fungoides (advanced stages)
- Advanced carcinoma of the testis
- Kaposi's Sarcoma
- Letterer-Siwe disease (histiocytosis-X)

2. Less Frequently Responsive Malignancies

- Choriocarcinoma resistant to other neoplastic drugs
- Cancer of the breast (unresponsive to endocrine surgery and hormonal therapy)

The simultaneous use of several cancer chemotherapy drugs is common practice. Generally, drugs with different dose-limiting clinical toxicities and different mechanisms of action are selected in order to obtain an increase in therapeutic response without added toxicity. Rarely is it possible to obtain equally as good a response with single antineoplastic treatment. Therefore, vinblastine is often part of polychemotherapy because, at the recommended doses, it does not cause significant suppression of the bone marrow or neuropathy. This approach to multiple treatment has been used in the chemotherapy of Hodgkin's disease.

Hodgkin's disease

Vinblastine has been found to be one of the most effective single antineoplastic agents for the treatment of Hodgkin's disease. Successful treatment of advanced Hodgkin's disease has been accomplished by the use of various multiple-drug regimens that have included vinblastine. Patients who have relapsed following treatment with the MOPP-regimen (mechlorethamine hydrochloride [nitrogen mustard], vincristine sulfate, prednisone and procarbazine) have often responded to combination drug therapy that included vinblastine. An alternative therapy that has been used in previously untreated patients with advanced Hodgkin's disease employs cyclophosphamide in place of nitrogen mustard and vinblastine instead of vincristine.

Advanced testicular germinal-cell cancers such as embryonal carcinoma, teratocarcinoma, and choriocarcinoma have been shown to be sensitive to vinblastine alone but a more satisfactory clinical response may be obtained by the concomitant administration of vinblastine with other anti-tumor drugs. The efficacy of bleomycin has been found to be enhanced if vinblastine is given 6 - 8 hours prior to bleomycin. This procedure appears to result in more cells being arrested during metaphase, the stage of cell division in which bleomycin is active.

CONTRAINDICATIONS

The use of vinblastine is contraindicated in patients with leukopenia. Vinblastine should not be administered to patients with bacterial infections. Such infections must be brought under control by the use of antibiotic or antiseptic therapy prior to the initiation of vinblastine treatment.

Pregnancy

Although no abnormalities of the human fetus have been associated with the use of vinblastine, information on its use during pregnancy is limited. Animal studies suggest that vinblastine may be teratogenic. Therefore, the use of vinblastine during pregnancy is contraindicated unless the expected benefits clearly outweigh the risk of side effects.

WARNINGS

Aspermia has been reported in man. Animal studies have demonstrated degenerative changes in germ cells and arrest of cell division in metaphase.

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

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

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.

Vinblastine used as part of a combination regimen with mitomycin may result in fatal acute respiratory distress or failure (see DRUG INTERACTIONS).

Particular caution is warranted when vinblastin is used in combination with other agents known to be ototoxic (see DRUG INTERACTIONS).

PRECAUTIONS

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, 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 leukopenia with less than 2,000 white blood cells per mm³ develops following administration of vinblastine, the patient should be monitored carefully for evidence of infection until the white blood cell count returns to normal.

If cachexia or skin ulcers are present, a more profound leukopenia response to the drug may occur. Therefore the use of vinblastine should be avoided in elderly persons with either of these conditions.

The thrombocyte count is not usually significantly lowered by therapy with vinblastine. In patients with malignant-cell infiltration of the bone marrow, the leukocyte and platelet counts have occasionally fallen precipitously after moderate doses of vinblastine and the administration of additional doses of vinblastine in such patients is not recommended.

The use of daily low doses of vinblastine for prolonged periods is not recommended, even though the total weekly dosage may be similar to the recommended treatment regimen. Little or no added therapeutic benefit has been demonstrated with the use of such low-dose regimens. Strict adherence to the recommended dosage schedule is very important. When vinblastine was given in 7 daily injections at a total dose equal to several times the recommended weekly dosage for prolonged periods, convulsions, severe and permanent central nervous system damage and even death occurred.

Avoid contamination of the eye with vinblastine solutions. If accidental contamination does occur, severe irritation may result and if the drug was given under pressure, corneal ulceration may result. The eye should be washed immediately with copious quantities of water.

DRUG INTERACTIONS

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 edema 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 or MV). Dyspnea 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 dyspnea, requiring chronic therapy, may occur. Vinblastine should not be readministered.

The simultaneous oral or intravenous administration of phenytoin and antineoplastic chemotherapy combinations that included vinblastine 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.

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 with an inhibitor of this metabolic pathway may cause an earlier onset and/or an increased severity of side effects, such as neurotoxicity.

Particular caution is warranted when vinblastine 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.

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), following coadministration of vinblastine, bleomycin and cisplatin.

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

ADVERSE REACTIONS

System Organ Class	Adverse Drug Reactions
Blood and lymphatic system disorders	Neutropenia
Endocrine disorders	Inappropriate anti-diuretic hormone secretion
Nervous system disorders	Cerebrovascular accident ^a
Ear and labyrinth disorders	VIIIth nerve injury ^b , ototoxicity
Cardiac disorders	Myocardial infarction ^a
^a in combination chemotherapy with vinblastine, 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.	

Leukopenia

Bone-marrow depression, especially leukopenia, is the most common adverse effect with vinblastine and tends to be dose-limiting. Before administering the drug, patients should be advised of the possibility of adverse reactions. Maximum depression occurs 4 - 10 days after administration, with recovery in one to three weeks.

Except for epilation and leukopenia the adverse reactions seen with vinblastine usually do not persist for more than 24 hours.

Gastrointestinal

Nausea, vomiting, constipation, vesiculation of the mouth, ileus, diarrhea, anorexia, abdominal pain, rectal bleeding, pharyngitis, hemorrhagic enterocolitis and bleeding from a dormant peptic ulcer may occur.

Neurologic

Neurologic effects can involve the autonomic nervous system and include malaise, headache, depression, psychoses, paresthesia, neuromyopathy, loss of deep tendon reflexes, peripheral neuritis, constipation, numbness and convulsions.

Miscellaneous

Epilation, malaise, weakness, dizziness, pain at the site of the tumor, and vesiculation of the skin may occur. Epilation is frequently not complete and in some instances hair re-growth will occur even though therapy continues.

Cellulitis and phlebitis may result if extravasation occurs during intravenous injection. If the extravasation is excessive, sloughing may occur.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Side effects are dose-related. Thus, patients can expect to experience these effects in an exaggerated manner if more than the recommended dose of vinblastine is given. As well, neurotoxicity may occur similar to that seen with vincristine sulfate. Management of suspected over-dosage of vinblastine should include the following:

1. Administer an antiemetic drug which usually controls nausea and vomiting.
2. Administer phenobarbital in anti-convulsant doses.

3. Be alert for the development of ileus which may necessitate non-surgical decompression of the gastrointestinal tract.
4. Monitor the patient's cardiovascular system.
5. Carry out daily blood counts as a guide for transfusion requirements. The most serious effect of an excessive dose of vinblastine, which may be life-threatening, is granulopoiesis.

DOSAGE AND ADMINISTRATION

There are variations in the depth of the leukopenic response which follows therapy with vinblastine. For this reason, it is recommended that the drug be given no more frequently than once every 7 days. It is wise to initiate therapy with a single intravenous dose of 3.7 mg/m² of body surface area (bsa). Thereafter, white blood cell counts should be made to determine the patient's sensitivity to vinblastine.

A simplified and conservative incremental approach to dosage at weekly intervals may be outlined as follows:

First Dose:

Adults: 3.7 mg/m² bsa

Children: 2.5 mg/m² bsa

Second Dose:

Adults: 5.5 mg/m² bsa

Children: 3.75 mg/m² bsa

Third Dose:

Adults: 7.4 mg/m² bsa

Children: 5.0 mg/m² bsa

Fourth Dose:

Adults: 9.25 mg/m² bsa

Children: 6.25 mg/m² bsa

Fifth Dose:

Adults: 11.1 mg/m² bsa

Children: 7.5 mg/m² bsa

The above-mentioned increases may be used until a maximum dose (not exceeding 18.5 mg/m² bsa for adults and 12.5 mg/m² bsa for children) is reached. The dose should not be increased after that dose which has reduced the white cell count to approximately 3,000 cells/mm³. In some adults, 3.7 mg/m² bsa may produce this leukopenia. Other adults may require more than 11.1 mg/m² bsa and, very rarely, as much as 18.5 mg/m² bsa may be necessary. For most adult patients, however, the weekly dosage will prove to be 5.5 to 7.4 mg/m² bsa.

When the dose of vinblastine which will produce the above degree of leukopenia has been established, a dose one increment smaller than this should be administered at weekly intervals for maintenance. Thus, the patient is receiving the maximum dose that does not cause leukopenia. It should be emphasized that, even though 7 days have elapsed, the next dose of vinblastine should not be given until the white cell count has returned to at least 4,000/mm³. In some cases, oncolytic activity may be encountered before leukopenic effect. When this occurs, there is no need to increase the size or subsequent doses.

The duration of maintenance therapy varies according to the disease being treated and the combination of antineoplastic agents being used. There are differences of opinion regarding the duration of maintenance therapy with the same protocol for a particular disease; for example, various durations have been used with the MOPP program in treating Hodgkin's disease. 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. In some disorders, survival following complete remission

may not be as prolonged as that achieved with shorter periods of maintenance therapy. On the other hand, failure to provide maintenance therapy in some patients may lead to unnecessary relapse. Failure to provide maintenance therapy for at least two years after complete remission in patients with testicular cancer often results in early relapse.

The dose of vinblastine (calculated to provide the desired amount) may be injected either into the tubing of a running intravenous infusion or directly into a vein. The latter procedure is readily adaptable to out-patient therapy. In either case, the injection may be completed in about one minute. If care is taken to ensure that the needle is securely within the vein and that no solution containing vinblastine is injected extravascularly, cellulitis and/or phlebitis will not occur.

To further minimize the possibility of extravascular spillage, it is suggested that the syringe and needle be rinsed with venous blood before withdrawal of the needle. The dose should not be diluted in large volumes of diluent (i.e. 100 to 250 mL) or given intravenously for prolonged periods (ranging from 30 to 60 minutes or more), since this frequently results in irritation of the vein and increases the chances of extravasation.

Because of the enhanced possibility of thrombosis, it is considered inadvisable to inject a solution of vinblastine into an extremity in which the circulation is impaired or potentially impaired by such conditions as compressing or invading neoplasm, phlebitis or varicosity.

CAUTION

If leakage into the surrounding tissue should occur during intravenous administration of vinblastine, it may cause considerable irritation. The injection should be discontinued immediately and any remaining portion of the dose should then be introduced into another vein. Local injection of hyaluronidase and the application of moderate heat to the area of leakage help disperse the drug and are thought to minimize discomfort and the possibility of cellulitis.

STABILITY AND STORAGE RECOMMENDATIONS

Vinblastine Sulfate Injection should be stored at 2°C to 8°C. Protect solution from light and freezing.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used.

Single-use vials. Discard unused portion.

SPECIAL INSTRUCTIONS FOR HANDLING OF CYTOTOXIC DRUGS

The following are precautionary measures recommended in the handling and preparation of cytotoxic agents such as vinblastine:

1. The procedure should be carried out in a vertical laminar flow hood (Biological Safety Cabinet - Class II).
2. PVC gloves, safety glasses, disposable gowns and masks should be worn by personnel.
3. All vials, syringes, needles and other materials which have come in contact with vinblastine should be segregated and destroyed by incineration. Sealed containers may explode if a tight seal exists. If incineration is unavailable, neutralization using 5% sodium hypochlorite or 5% sodium thiosulfate should be carried out instead.
4. Bi-annual hematologic examinations should be performed on personnel regularly involved in the handling and preparation of vinblastine.

AVAILABILITY OF DOSAGE FORM

Vinblastine Sulfate Injection, 1 mg/mL, is available in single-use vials of 10 mg/10 mL, each wrapped in a clear plastic ONCO-TAIN[®] sleeve.

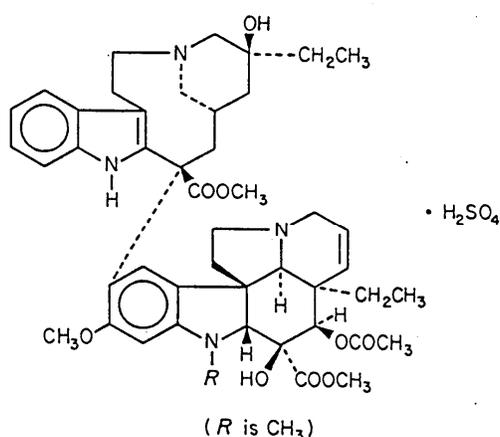
PHARMACEUTICAL INFORMATION

Drug substance

Proper Name: Vinblastine Sulfate

Chemical Name: Vincalokoblastine (VBL) Sulfate

Structural Formula:



Molecular Formula: C₄₆H₅₈O₉N₄·H₂SO₄

Molecular Weight: 909.07

Description: Vinblastine Sulfate is the sulfate salt of an alkaloid obtained from *Vinca rosea* Linn (a flowering herb commonly known as the periwinkle) or *Catharanthus roseus* G._Don. Vinblastine sulfate is a white to slightly yellow, odorless, hygroscopic amorphous or crystalline powder. It is soluble in water and methyl alcohol, slightly soluble in chloroform and alcohol and practically insoluble in ether.

Composition: Vinblastine Sulfate Injection contains 1 mg/mL of Vinblastine Sulfate with 0.9% Sodium Chloride in Water for Injection as a sterile unpreserved solution. Sodium Hydroxide and/or Sulphuric Acid as pH adjusters.

PHARMACOLOGY

Vinblastine, as with other Vinca alkaloids, has been shown to produce metaphase arrest both in tissue cultures and in the bone marrow of treated animals but, as these effects have been seen in tumors at dose levels at which the tumour is apparently not affected, the relationship between the action of the drugs as spindle poisons and the mechanism of their action as tumour inhibitors is questionable. Vinblastine has been shown to stimulate aerobic acid production without inhibiting respiration.

At high doses it has been shown to inhibit the synthesis of DNA in mouse tumour cells. As well, the profound effect on the turnover of soluble RNA in tumour cells by moderate doses of vinblastine may be of significance in explaining its antineoplastic activity.

It has been suggested that drugs that produce metaphase arrest may be of special value in combination therapy since the temporary synchronization of mitosis might cause the incorporation and increase the cells sensitivity to other cytotoxic drugs.

In addition to arresting mitosis at metaphase and inhibiting RNA synthesis, vinblastine sulfate may also interfere with amino acid metabolism. It has some immunosuppressant activity. Cross resistance with vincristine has been reported. The selective nature of the activity of vinblastine may be due to a number of factors involved with cell energy enzyme metabolism and membrane permeability.

PHARMACOKINETICS

In a pharmacokinetic study in three patients, elimination after I.V. injection was tri-phasic with mean half-lives of 3.9, 53, and 1173 minutes. Vinblastine was metabolized to des-acetyl-vinblastine probably in the liver. An I.V. dose of vinblastine, radioactively labeled in the indole aromatic ring was given to one patient. Total radioactivity excreted in the urine in 72 hours was 13.6%, and 9.9% was excreted in the feces in 72 hours. About 73% of the radioactivity remained in the body after 6 days.

Vinblastine is not reliably absorbed from G.I. tract. It rapidly disappears from the blood and penetrates poorly into the cerebrospinal fluid.

TOXICITY

Acute Toxicity

The mean (\pm SE) intravenous LD₅₀ of vinblastine in mice has been reported as being 17.47 ± 1.57 mg/kg (range: 11.99 ± 1.95 to 22.44 ± 3.56 mg/kg). The oral LD₅₀ as 33.12 ± 5.03 and intraperitoneal LD₅₀ as 3.2 ± 0.02 mg/kg.

In a comparative mouse study the I.V. LD₅₀ of Vinblastine for Injection B.P. (DBL) was found to be 13.84 mg/kg compared to 13.82 mg/kg (12.93 - 15.37 mg/kg) for Velbe, Lilly.

Toxicity studies in animals have shown that a single non-lethal injection of vinblastine depresses the granulocyte count without affecting the lymphocyte levels. Recovery of the peripheral blood count occurs within 4 - 5 days. Large doses of vinblastine result in death from leukopenia and pre-terminally, anorexia, weight loss and some diarrhea occurs. In mice the drug inhibits the response of the uterus to the action of estrogen, but folinic acid diminishes the effect. In dogs and mice the period of anesthesia and sleeping time produced by barbiturates is prolonged by vinblastine.

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Pfizer Canada ULC
Kirkland, Québec H9J 2M5