PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]Vinblastine Sulfate Injection

Sterile Solution, 1 mg/mL, Injection

Pfizer Standard

Antineoplastic Agent

ATC code: L01CA01

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

Date of Initial Authorization:
DEC 22, 1988

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Submission Control Number: 288620

RECENT MAJOR LABEL CHANGES

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Vinblastine Sulfate Injection (vinblastine sulfate) is indicated in the palliative treatment of the following neoplastic diseases:

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)
- Histiocytic lymphoma
- Mycosis fungoides (advanced stages)
- Advanced carcinoma of the testis
- Kaposi's Sarcoma
- Letterer-Siwe disease (histiocytosis-X)

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.

1.1 Pediatrics

Pediatrics: Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Vinblastine Sulfate Injection in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use (see **4 DOSAGE AND ADMINISTRATION**).

1.2 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see **7.1.4 Geriatrics**).

2 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 (see **7.1.1 Pregnant Women**).

Vinblastine Sulfate Injection is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

4 DOSAGE AND ADMINISTRATION

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.

4.1 Dosing Considerations

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/m^2 of body surface area (bsa). Thereafter, white blood cell counts should be made to determine the patient's sensitivity to vinblastine.

4.2 Recommended Dose and Dosage Adjustment

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

First Dose:
Adults: 3.7 mg/m^2 bsa
Children: 2.5 mg/m^2 bsa

Second Dose:
Adults: 5.5 mg/m^2 bsa
Children: 3.75 mg/m^2 bsa

Third Dose:
Adults: 7.4 mg/m^2 bsa
Children: 5.0 mg/m^2 bsa

Fourth Dose:
Adults: 9.25 mg/m^2 bsa
Children: 6.25 mg/m^2 bsa

Fifth Dose:
Adults: 11.1 mg/m^2 bsa
Children: 7.5 mg/m^2 bsa

The above-mentioned increases may be used until a maximum dose (not exceeding 18.5 mg/m^2 bsa for adults and 12.5 mg/m^2 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/mm^3. In some adults, 3.7 mg/m^2 bsa may produce this leukopenia. Other adults may require more than 11.1 mg/m^2 bsa and, very rarely, as much as 18.5 mg/m^2 bsa may be necessary. For most adult patients, however, the weekly dosage will prove to be 5.5 to 7.4 mg/m^2 bsa.

4.4 Administration

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/mm^3. 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.

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.

5 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Injection	single-use vials of 10 mg/10 mL	0.9% Sodium Chloride in Water for Injection as a sterile unpreserved solution. Sodium Hydroxide and/or Sulphuric Acid as pH adjusters.

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.

7 WARNINGS AND PRECAUTIONS

General

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.

Carcinogenesis and Mutagenesis

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.

Ear/Nose/Throat

Particular caution is warranted when vinblastine is used in combination with other agents known to be ototoxic (see **9 DRUG INTERACTIONS**).

Hematologic

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 mm^3 develops following administration of vinblastine, the patient should be monitored carefully for evidence of infection until the white blood cell count returns to normal.

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.

Hepatic/Biliary/Pancreatic
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.

Ophthalmologic
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.

Reproductive Health: Female and Male Potential

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 (see **2 CONTRAINDICATIONS, 7.1.1 Pregnant Women**).

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.

Fertility
Based on clinical reports, male and female fertility may be compromised. 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.

It is recommended to discuss fertility preservation with men and women prior to treatment (see **2 CONTRAINDICATIONS, 7.1.1 Pregnant Women**).

Respiratory
Vinblastine used as part of a combination regimen with mitomycin may result in fatal acute respiratory distress or failure (see **9 DRUG INTERACTIONS**).

7.1 Special Populations

7.1.1 Pregnant Women
Caution is necessary with the use of oncolytic drugs during pregnancy. Vinblastine sulfate can cause fetal harm when administered to a pregnant woman, although there are no adequate and well-controlled studies in pregnant women. Animal studies with vinblastine sulfate suggest that teratogenic

effects may occur. Laboratory animals given this drug early in pregnancy suffer resorption of the conceptus; surviving fetuses demonstrate gross deformities (see **2 CONTRAINDICATIONS**, **7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential**).

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 of to the fetus.

7.1.2 Breast-feeding

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.

7.1.3 Pediatrics

See **4 DOSAGE AND ADMINISTRATION**.

7.1.4 Geriatrics

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.

8 ADVERSE REACTIONS

Table 2. Adverse Drug Reaction Table

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], neurotoxicity
Ear and labyrinth disorders	VIII[th] cranial 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.

9 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.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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.

10.2 Pharmacodynamics

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 mm^3). 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.

10.3 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.

11 STORAGE, STABILITY AND DISPOSAL

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.

12 SPECIAL HANDLING INSTRUCTIONS

Vinblastine Sulfate injection is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing Vinblastine Sulfate injection solutions.

Vinblastine Sulfate injection should be administered only by or under the direct supervision of a qualified physician who is experienced in the use of cancer chemotherapeutic agents.

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.

Pregnant personnel are advised not to handle chemotherapeutic agents.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

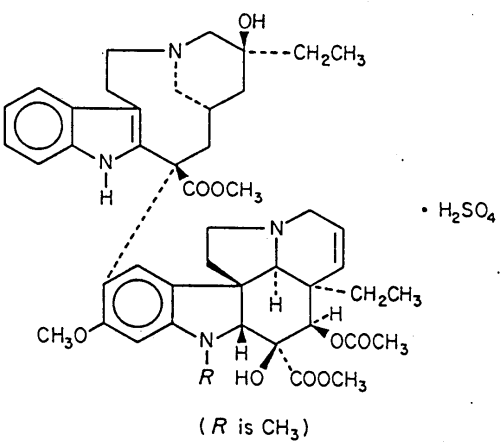
Drug Substance

Proper name: Vinblastine Sulfate

Chemical name: Vincaleukoblastine (VBL) Sulfate

Molecular formula and molecular mass: $C_{46}H_{58}O_9N_4.H_2SO_4$ and 909.07

Structural formula:



(*R* is CH_3)

Product Characteristics:
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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Acute Toxicity

The mean (+SE) intravenous LD_{50} 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 LD_{50} as 33.12 + 5.03 and intraperitoneal LD_{50} as 3.2 + 0.02 mg/kg.

In a comparative mouse study the I.V. LD_{50} 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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]Vinblastine Sulfate Injection

Read this carefully before you start taking **Vinblastine Sulfate Injection** and each time you get an injection. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Vinblastine Sulfate Injection**.

What is Vinblastine Sulfate Injection used for?

Vinblastine Sulfate Injection is used in the treatment of cancers of the:

- lymph nodes
- spleen
- bone marrow
- testicles
- ovaries
- skin
- breast
- placenta

It may be given alone or in combination with other anti-cancer medicines.

How does Vinblastine Sulfate Injection work?
Vinblastine Sulfate Injection belongs to a group of medicines called antineoplastics or cytotoxics.

The medicinal ingredient, vinblastine sulfate, is a *vinca alkaloid* which is an anti-cancer medicine. Treatment with an anti-cancer medicine is sometimes called cancer chemotherapy.

Vinblastine Sulfate Injection works by interfering with the growth and proliferation of cancer cells and ultimately leading to their destruction.

What are the ingredients in Vinblastine Sulfate Injection?

Medicinal ingredients: vinblastine sulfate.
Non-medicinal ingredients: sodium chloride, sodium hydroxide, sulphuric acid and water for injection.

Vinblastine Sulfate Injection comes in the following dosage forms:
Solution; 1 mg / mL

Do not use Vinblastine Sulfate Injection if:

- your blood tests show that you do not have enough white blood cells to fight infection (unless this is a result of your condition being treated).
- you have a bacterial infection which is not under control.

- you are pregnant, think you might be pregnant, plan to become pregnant or father a child. Vinblastine Sulfate Injection may cause birth defects if either the male or the female partner is undergoing treatment at the time of conception.
- you are allergic to vinblastine sulfate or any of the other ingredients of this medicine (see **What are the ingredients in Vinblastine Sulfate Injection?**).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Vinblastine Sulfate Injection. Talk about any health conditions or problems you may have, including if you:

- are given daily low doses of Vinblastine Sulfate Injection for prolonged periods.
- have ever had leukemia or undergone radiation therapy.
- are given other agents known to be harmful to the ears or auditory system.
- have an abnormal blood cell count.
- have liver disease, including inflammation of the liver (hepatitis) or yellowing of your skin or the whites of your eyes (jaundice) or loss of appetite.
- are also being treated with mitomycin, another anti-cancer medicine. The combination with Vinblastine Sulfate Injection can cause serious breathing problems leading to death.
- are an elderly patient in poor health or with skin sores.

Other warnings you should know about:

Pregnancy and Breastfeeding:

Female patients:
- You should not get pregnant while you are being treated with Vinblastine Sulfate Injection.
- You must use effective birth control during treatment and for at least 7 months after treatment.
- Talk to your healthcare professional immediately if you become pregnant while being treated with Vinblastine Sulfate Injection or within 7 months of your last dose.
- It is not known if Vinblastine Sulfate Injection passes into breastmilk. You should not breastfeed while you are being treated with Vinblastine Sulfate Injection and for 1 week after your last dose. Talk to your healthcare professionals about other ways to feed your baby during this time.

Male patients:
- You must use effective birth control during treatment and for at least 4 months after treatment if you have a female partner that could become pregnant.
- Talk to your healthcare professional immediately if your female partner becomes pregnant while you are being treated with Vinblastine Sulfate Injection or within 4 months of your last dose.

Fertility: Vinblastine Sulfate Injection can affect fertility in both male and female patients. It can reduce the production and motility of semen in men. It can cause an absence of periods in women. Talk to your healthcare professional about ways to preserve your fertility before you start treatment with Vinblastine Sulfate Injection.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Vinblastine Sulfate Injection:

- The use of mitomycin with or without progesterone (anti-cancer medicines) with Vinblastine Sulfate Injection may cause severe breathing problems especially if you have a pre-existing heart condition.
- Vinblastine Sulfate Injection may reduce the effectiveness of medicines used to treat epilepsy, in particular, blood levels of phenytoin may need to be monitored more frequently.
- The use of medicines that slow down the breakdown of drugs by the liver, particularly those affecting the enzyme CYP 3A, requires caution, especially if you have liver problems. When Vinblastine Sulfate Injection is taken with such medicines, there is a risk of nerve damage.
- The use of Vinblastine Sulfate Injection alongside other medicines known to cause ear or hearing problems, such as platinum-containing cancer treatments, requires special care and attention.
- The use of bleomycin or cisplatin (anti-cancer medicines) with Vinblastine Sulfate Injection may cause heart and circulation problems, worsening of low white blood cell counts, decrease in kidney function, nervous system problems, hearing problems, impaired balance and changes to sperm motility.
- The use of erythromycin (antibiotic) may increase the side effects of Vinblastine Sulfate Injection such as low levels of white blood cells, muscle pain and constipation.

How to take Vinblastine Sulfate Injection:

- **Vinblastine Sulfate Injection should only be prescribed by a healthcare professional who is experienced with the use of anti-cancer medicines.**
- Vinblastine Sulfate Injection will be given to you by a healthcare professional in a healthcare setting.
- This medicine will only be given into a vein. It is given by an infusion (drip) or an injection (using a syringe).
- Vinblastine Sulfate Injection is an irritant. If it accidentally gets into your eyes, tell your healthcare professional immediately so that it may be washed out.
- Your healthcare professional will do blood tests once or twice weekly while you are being treated with Vinblastine Sulfate Injection and will adjust your dose or stop treatment, if needed, based on the results.

Usual dose:
Your healthcare professional will decide on the dose of Vinblastine Sulfate Injection that is right for you and how often it must be given.

Your dose will depend on your medical condition, your size and how well your liver is working. Your healthcare professional will see how well your liver is working using a blood test. If your liver is not working properly the dose may be reduced.

Vinblastine Sulfate Injection is usually given once a week.

Overdose:
It is unlikely that you will receive too much Viinblastine Sulfate Injection as you will be closely monitored by your healthcare professionals during your injection.

If you think you, or a person you are caring for, have been given too much Vinblastine Sulfate Injection, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to go back for your next dose at the scheduled time, talk to your healthcare professional.

What are possible side effects from using Vinblastine Sulfate Injection?
These are not all the possible side effects you may have when taking Vinblastine Sulfate Injection. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Blistering of the skin, skin ulcers
- Mouth ulcers
- Sore throat
- Significant weight loss/loss of appetite
- Dizziness
- Numbness or tingling in fingers and toes ("pins and needles")
- Stomach cramps, constipation or diarrhea
- Nausea or vomiting (feeling or being sick)
- Pain in the chest, jaw, bones or where the tumor is
- Headache
- Difficulty with balance
- Uncontrolled movements of the eyes
- Shortness of breath, wheezing
- Dry cough
- Weakness
- Tiredness and generally feeling unwell
- Hair loss

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Get immediate medical help**
	Only if severe	**In all cases**	
UNKNOWN FREQUENCY			
Depression (sad mood that won't go away)**:** difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities		**√**	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Get immediate medical help**
	Only if severe	**In all cases**	
with friends, reduced libido (sex drive) and thoughts of death or suicide			
Gastrointestinal problems: stomach pain, blood in the stool, rectal bleeding		**√**	
Hearing problems: ear pain, hearing loss		**√**	
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations		**√**	
Injection site reaction: blistering, itching, pain, redness, severe skin damage, tenderness, warmth in the area around the injection		**√**	
Leukopenia (low white blood cells): signs of infection such as a sore throat and high temperature, fatigue, aches and flu-like symptoms		**√**	
Liver problems: yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, pale stool, unusual tiredness		**√**	
Myelosuppression (decrease in bone marrow function which can affect the production of blood cells)		**√**	
Myocardial infarction (heart attack): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint, irregular heartbeat			**√**

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Get immediate medical help**
	Only if severe	**In all cases**	
Neurotoxicity (damage to the nervous system): agitation, blurred vision, confusion, convulsions, difficulty speaking, dizziness, hallucinations, headache, impaired thinking, loss of control of body movements, loss of tendon reflexes, memory loss, mental status changes, nervousness, numbness and tingling, vision loss, muscle weakness, seizures			√
Seizures (fit): uncontrollable shaking with or without loss of consciousness			√
Stroke (bleeding or blood clot in the brain)**:** sudden numbness, weakness or tingling of the face, arm, or leg, particularly on one side of the body, sudden headache, blurry vision, difficulty swallowing or speaking, lethargy, dizziness, fainting, vomiting, trouble understanding, trouble with walking and loss of balance			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Vinblastine Sulfate Injection will be stored at the hospital by your healthcare professional.

Keep out of reach and sight of children.

Store in a refrigerator (2°C - 8°C). Do not freeze

Store in the original carton in order to protect from light.

If you want more information about Vinblastine Sulfate Injection:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website:

{https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.pfizer.ca, or by calling Pfizer Canada ULC, at: 1-800-463-6001 (Medical Information).

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