

Vinblastina Kemex
Vinblastine Sulfate 10 mg
Injectable lyophilized

Rx Only
Made in Argentina
Formula:
Each vial contains:

Vinblastine Sulfate.....10.0 mg
Lactose monohydrate..... 50.0 mg
Mannitol..... 50.0 mg

THERAPEUTIC ACTION

Antineoplastic Agents

Vinblastine sulfate is an alkaloid of Vinca rosae Linn

ATC Code : L01CA01

Structural and molecular formula: C₄₆H₅₈N₄O₉H₂SO₄

PHARMACOLOGY

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.

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.

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; carcinoma of the breast, unresponsive to appropriate endocrine surgery and hormonal therapy.

One of the most effective single agents for 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.

CONTRAINDICATIONS

Vinblastine is contraindicated in patients who have experienced hypersensitivity reactions with this drug.

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.

WARNINGS

Vinblastine must be used only by physicians experienced in cytotoxic chemotherapy.

This preparation is for intravenous use only.

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

As with other antineoplastic agents, Vinblastine Injection may cause a severe local reaction on extravasation. If leakage into the surrounding tissue should occur during intravenous administration of vinblastine, the 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.

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

Liver disease may alter the elimination of vinblastine in the bile, markedly increasing toxicity to peripheral nerves and necessitating a dosage modification in affected patients.

PRECAUTIONS

Patients should be carefully monitored for infection until white cell count has returned to normal levels if leukopaenia with less than 2.0 x 10⁹ white blood cells per litre (2000/mm³) occurs following a dose of Vinblastine Injection.

When cachexia or ulcerated areas of the skin surface are present, there may be more profound leukopaenic response to the drug; therefore its use should be avoided in older persons suffering from either of these conditions.

Leucocyte and platelet counts have sometimes fallen precipitously after moderate doses of Vinblastine Injection in patients with malignant-cell infiltration of the bone marrow. Further use of the drug in such patients is inadvisable.

The use of small amounts of Vinblastine Injection daily for long periods of time is not advised, since little or no added therapeutic effect has been demonstrated, even though the resulting total weekly dosage may be similar.

It is important to strictly adhere to the recommended dosage schedule.

Convulsions, severe and permanent central nervous system damage and even death have occurred when amounts of several times the recommended weekly dosage were given in 7 daily instalments for long periods.

Avoid contamination of the eye with Vinblastine Injection. If accidental contamination occurs, severe irritation (or corneal ulceration if delivered under pressure) may result. Wash the eye with water immediately and thoroughly.

A risk-benefit assessment should be considered when the following medical problems exist in patients who are to receive Vinblastine Injection: chicken pox (existing or recent exposure), herpes zoster, gout or a history of urate renal stones, impaired hepatic function and infection.

USE IN PREGNANCY

Category D. This category includes drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Consult literature for further information.

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

USE IN LACTATION

Although very little information is available regarding excretion of anti-neoplastic agents in breast milk, breast-feeding is not recommended while vinblastine is being administered because of the risks to the infant.

DRUG INTERACTIONS

Caution should be exercised with the concomitant administration of Vinblastine Injection with bone marrow suppressant drugs such as azathioprine, interferon, chloramphenicol, amphotericin B, colchicine, flucytosine and zidovudine.

The simultaneous oral or intravenous administration of phenytoin and antineoplastic chemotherapy combinations that included Vinblastine Injection have been reported to have reduced blood levels of phenytoin and to have increased seizure activity. Dosage adjustment should be based on phenytoin blood level monitoring. The contribution of vinblastine to this interaction is not certain. The interaction may result from either reduced absorption of phenytoin or an increase in the rate of its metabolism and elimination.

Immunisation with live vaccines in patients being treated with Vinblastine Injection may result in a potentially life-threatening infection. The immune response of the body is suppressed by vinblastine. The effectiveness of the vaccine may be poor and generalised infection may occur in patients immunised with live vaccines. Live vaccines should not be administered to patients being treated with vinblastine.

The chemotherapy drug regimen of vinblastine, bleomycin and cisplatin appears to cause serious life- threatening cardiovascular toxicity. One report describes five patients under treatment for germ cell tumours who died from acute life-threatening vascular events (myocardial infarction, rectal infarction, cerebrovascular accident) following VBP therapy. This drug combination is very effective in the treatment of testicular carcinoma but its potential toxicity is serious.

There are several reports describing an increase in lung disease in patients treated with a combination of vinblastine and mitomycin. Diffuse lung damage characterised by interstitial infiltrates and pleural effusions resulting in respiratory distress and cough have been described after treatment with vinblastine. The potential hazards of combining vinblastine and mitomycin necessitate the avoidance of this combination.

ADVERSE REACTIONS

Patients should be advised of the possibility of untoward symptoms before the use of this product.

The incidence of side effects with use of vinblastine appears to be dose related. In general most side effects do not persist longer than 24 hours. Neurologic effects are not common but can occur and may last for more than 24 hours. Leukopenia, the most common side effect, is usually the dose limiting factor.

Side effects reported have been:

Haematological: Leukopenia, anaemia, thrombocytopenia.

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

Neurologic: Numbness, paraesthesiae, peripheral neuritis, mental depression, loss of deep tendon reflexes, headache, convulsions.

Miscellaneous: Malaise, weakness, dizziness, pain in tumour site, vesiculation of the skin, hypertension, bone pain, jaw pain, Raynaud's phenomenon, inappropriatesecretion of antidiuretic hormone (high dose), hypersensitivity reactions.

Antiemetic drugs may be used to control nausea and vomiting.

Alopecia is common. The development of epilation is usually not total and in some cases hair regrows during the continuance of maintenance therapy.

Extravasation during intravenous injection may lead to cellulitis and phlebitis. If amount of extravasation is great, sloughing may occur.

DOSAGE AND ADMINISTRATION

Vinblastine Injectable lyophilized is for intravenous use only. 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 injected.

Preparation of the Reconstituted:

Sterile Vinblastine Sulfate is reconstituted for intravenous use by adding 10 ml of 0.9% sodium chloride (no other solution is recommended) to the 10 mg vial, to produce a solution containing 1 mg/ml of Vinblastine Sulfate. When the solution is prepared, the container or the syringe with the individual dose prepared to be administered to the patient, should be placed until it is used, in a sterile bag with the following label: DO NOT REMOVE THE COVER UNTIL THE INJECTION TIME IF IT IS ADMINISTERED INTRATHECALLY CAUSES DEATH. ONLY FOR INTRAVENOUS USE. It is recommended that Vinblastine Injection be administered ONCE EVERY 7 DAYS. Therapy is initiated in adults by the administration of a single intravenous dose of 3.7 mg/m² bsa (body surface area). Thereafter white blood cell counts should be made to determine the patient's sensitivity to vinblastine.

Recommended incremental approach to dosage at WEEKLY INTERVALS as follows:

	Adults mg/m ² bsa	Children mg/m ² bsa
First dose	3.7	2.5
Second dose	5.5	3.75
Third dose	7.4	5.0
Fourth dose	9.25	6.25
Fifth dose	11.1	7.5

Dosage increase may be continued but must not exceed 18.5 mg/m² bsa for adults and 12.5 mg/m² bsa for children. Dosage should not be increased after the dose which reduces white cell count to approximately 3.0 x 10⁹/L (3000/mm³).

For most adult patients the dosage will be 5.5 to 7.4 mg/m² bsa. However, leukopenia can be produced at 3.7 mg/m² bsa; others may require 11.1 mg/m² bsa, and very rarely 18.5 mg/m² bsa.

A maintenance dosage is administered ONCE WEEKLY, one increment smaller than the dosage to produce the above degree of leukopenia. Hence, the patient is receiving the maximum dosage that does not cause leukopenia.

IT SHOULD BE EMPHASIZED THAT, EVEN THOUGH 7 DAYS HAVE ELAPSED, THE NEXT DOSE OF VINBLASTINE INJECTABLE LYOPHILIZED SHOULD NOT BE GIVEN UNTIL THE WHITE CELL COUNT HAS RETURNED TO AT LEAST 4.0 x 10⁹/L (4000/mm³). In some cases, oncolytic activity may be encountered before leukopenic effect. When this occurs, there is no need to increase the size of subsequent doses.

Maintenance therapy duration is dependent upon the disease being treated and the antineoplastic agent combination. Maintenance therapy for 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.

ADMINISTRATION

The calculated dose of the solution may be injected either directly into the vein or into the injection site of a running intravenous infusion.

Care should be taken to avoid infiltration of subcutaneous tissues (SEE WARNINGS).

Vinblastine Injectable lyophilized may be further diluted with compatible solutions (0.9% saline for the purpose of I.V. infusion. However, dilution in large volumes of diluent (100-250 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.

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

OVERDOSAGE

Clinical Features

The symptoms of overdosage are likely to be an extension of vinblastine's pharmacological action. Possible symptoms of toxicity are those listed under adverse reactions.

The major effect of toxic doses of Vinblastine Injectable Lyophilized will be myelosuppression and this may be life threatening.

Management

Symptomatic supportive measures should be instituted. Particular attention should be given to prevention and treatment of possible severe infections secondary to severe, persistent bone marrow depression. Specialist texts should be consulted.

STORAGE

Vinblastine Injectable Lyophilized should be stored at 2-8°C.

Period of validity

2 years

KEEP OUT OF THE REACH OF CHILDREN.

"This medication must be used under medical prescription and may not be repeated without a new prescription"

Medicament Authorized by the Health Ministry Certificate: N° 57.494
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