VINBAS™

Vinblastine Sulfate USP IV Injection

DESCRIPTION

Vinbas™ injection is a preparation of Vinblastine Sulfate. Vinblastine Sulfate is a selective mitotic inhibitor of certain malignant cells and as such appears to be different from other recognized antineoplastic drugs. Vinblastine interferes with cell metabolism and the entrance of glutamic acid into the citric acid cycle and to urea. 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. 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.

INDICATIONS

Vinbas™ injection 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)
- Histolocytic 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)

DOSAGE AND ADMINISTRATION

Dosage:

It is recommended that **Vinbas**™ injection 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 **Vinbas**™ Injection. A simplified and conservative incremental approach to dosage at weekly intervals may be outlined 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

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.

When the dose of **Vinbas**™ injection 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 **Vinbas**™ 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.

Administration:

The dose of **Vinbas**™ (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 **Vinbas**™ 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.

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)

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 antibiotics or antiseptics before the initiation of therapy with Vinblastine.

SIDE EFFECTS

- **Leukopenia** (most common adverse effect)
- **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.
- **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.

PRECAUTIONS AND WARNINGS

The dose-limiting factor is myelosuppression. In general, the larger the dose employed, the more profound and longer lasting the leucopenia will be. 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. 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. 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. 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.

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. 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. Particular caution is warranted when Vinblastine is used in combination with other agents known to be ototoxic.

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.

USE IN PREGNANCY AND LACTATION

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.

Very little information is available regarding excretion of anti-neoplastic agents in breast milk. It is not known whether Vinblastine Sulfate is excreted in human milk. Breast-feeding is not recommended while Vinblastine is being administered because of the risks to the infant. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

DRUG INTERACTION

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. 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 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.

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

OVERDOSE

The symptoms of overdosage are likely to be an extension of Vinblastine's pharmacological action. 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.

PHARMACEUTICAL PRECAUTION

Store in a refrigerator 2 °C to 8 °C temperature. Keep away from light & wet place. Keep out of reach of children.

PACKAGING

Vinbas™ IV injection: Each box contains one vial of Vinblastine Sulfate USP 10 mg in10 mL solution (1 mg/mL).

SK+F ONCOLOGY
Manufactured by
ESKAYEF PHARMACEUTICALS LTD.
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