Velvin

Vinblastine Sulfate Injection

COMPOSITION
Velvin Injection: Each 10 ml contains Vinblastine Sulfate USP 10 mg.

CLINICAL PHARMACOLOGY
Vinblastine Sulfate is a statokinetic oncolytic agent. When treated in vitro with this preparation, growing cells are arrested in metaphase. It is a vinca alkaloid and a chemical analogue of vincristine. It binds tubulin, thereby inhibiting the assembly of microtubules. Vinblastine treatment causes M phase specific cell cycle arrest by disrupting microtubule assembly and proper formation of the mitotic spindle and the kinetochore, each of which are necessary for the separation of chromosomes during anaphase of mitosis. Tissue-culture studies suggest an interference with metabolic pathways of amino acids leading from glutamic acid to the citric acid cycle and to urea. A number of studies in vitro and in vivo have demonstrated that Vinblastine Sulfate produces a statokinetic effect and various atypical mitotic figures.

Pharmacokinetics
Absorption
Rapidly absorbed 15 to 30 min following IV triphasic serum decay pattern.

Distribution
Undergoes rapid distribution (from blood to tissue) and extensive tissue binding. The volume of the central compartment is 70% of body weight, probably reflecting very rapid tissue binding to formed elements of the blood.

Metabolism
Metabolized by the hepatic P450 3A cytochromes. The metabolite, deacetyl vinblastine, is more active than parent drug.

Elimination
Major route of excretion is biliary system. Terminal t½ is 24.8 hour.

INDICATIONS
Hodgkin's Disease
Vinblastine Sulfate has been shown to be one of the most effective single agents for the treatment of Hodgkin's disease. Advanced Hodgkin's disease has also been successfully treated with several multiple-drug regimens that included Vinblastine Sulfate. Patients who had relapses after treatment with the MOPP program—mechlorethamine hydrochloride (nitrogen mustard), vincristine sulfate, prednisone and procarbazine—have likewise responded to combination-drug therapy that included Vinblastine Sulfate. A protocol using cyclophosphamide in place of nitrogen mustard and Vinblastine Sulfate instead of vincristine sulfate is an alternative therapy for previously untreated patients with advanced Hodgkin's disease. Advanced testicular germinal-cell cancers (embryonal carcinoma, teratocarcinoma and choriocarcinoma) are sensitive to Vinblastine Sulfate alone, but better clinical results are achieved when Vinblastine Sulfate is administered concomitantly with other antineoplastic agents. The effect of bleomycin is significantly enhanced if Vinblastine Sulfate is administered six to eight hours prior to the administration of bleomycin; this schedule permits more cells to be arrested during metaphase, the stage of the cell cycle in which bleomycin is active.

Vinblastine Sulfate Injection is indicated in the palliative treatment of the following

I. Frequently Responsive Malignancies
- Generalized Hodgkin's disease (Stages III and IV, Ann Arbor modification of Rye staging system)
- Lymphocytic lymphoma (nodular and diffuse, poorly and well differentiaed)
- Histiocytic lymphoma
- Mycosis fungoides (advanced stages)
- Advanced carcinoma of the testis
- Kaposi's sarcoma
- Letterer-Siwe disease (histiocytosis X)

II. Less Frequently Responsive Malignancies
- Choriocarcinoma resistant to other chemotherapeutic agents
- Carcinoma of the breast, unresponsive to appropriate endocrine surgery and hormonal therapy

DOSAGE AND ADMINISTRATION

Initial Therapy

Adults
IV Initially 3.7 mg/m^2 as a single dose/week. Then increase at weekly intervals in 1.8 mg/m^2 increments until the leukocyte count decrease to about 3,000/mm^3. The maximum weekly dose is 18.5 mg/m^2 .

Pediatric
IV Initially 2.5 mg/m^2 as a single dose/week. Then increase at weekly intervals in 1.25 mg/m^2 increments until the leukocyte count decrease to about 3,000/mm^3. The maximum weekly dose is 12.5 mg/m^2.

Maintenance Therapy

Adults
IV maintenance dose is 1.8 mg/m^2 less than the dose required to produce a leukocyte count of 3,000/mm^3 every 7 to 14 days. The optimum weekly dose is normally 5.5 to 7.4 mg/m^2. Maintenance doses should not be given until the WBC reaches 4,000/mm^3.

Children
IV maintenance dose is 1.25 mg/m2 less than the dose required to produce a leukocyte count of 3,000/mm^3 every 7 to 14 days. Maintenance doses should not be given until the WBC reaches 4,000/mm^3.

Caution for administration
It is extremely important that the intravenous needle or catheter be properly positioned before any Vinblastine Sulfate is injected. Leakage into surrounding tissue during intravenous administration of Vinblastine Sulfate may cause considerable irritation. If extravasation occurs, 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 will help disperse the drug and may minimize discomfort and the possibility of cellulitis.There are variations in the depth of the leukopenic response that follows therapy with Vinblastine Sulfate. For this reason, it is recommended that the drug be given no more frequently than once every 7 days.

Dosage Adjustment for Patients with Leukopenia
When the dose of Vinblastine Sulfate which will produce the above degree of leukopenia has been established, a dose of 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 seven days have elapsed, the next dose of Vinblastine Sulfate 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 of subsequent doses.

Dosage Adjustment for Patients with Hepatic Impairment
A reduction of 50% in the dose of Vinblastine Sulfate is recommended for patients having a direct serum bilirubin value above 3 mg/100 mL. Since metabolism and excretion are primarily hepatic, no modification is recommended for patients with impaired renal function.

CONTRAINDICATIONS
Vinblastine Sulfate is contraindicated in patients who have significant granulocytopenia unless this is a result of the disease being treated. It should not be used in the presence of bacterial infections. Such infections must be brought under control prior to the initiation of therapy with Vinblastine Sulfate.

WARNINGS
This preparation is for intravenous use only. It should be administered by individuals experienced in the administration of Vinblastine Sulfate. The intrathecal administration of Vinblastine Sulfate usually results in death. After inadvertent intrathecal administration of vinca alkaloids, immediate neurosurgical intervention is required in order to prevent ascending paralysis leading to death. In a very small number of patients, life-threatening paralysis and subsequent death was averted but resulted in devastating neurological sequelae, with limited recovery afterwards.

If Vinblastine Sulfate is mistakenly given by the intrathecal route, following treatment should be initiated immediately after injection:

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

2. Insertion of an epidural catheter into the subarachnoid space via the intervertebral space above initial lumbar access and CSF irrigation with lactated Ringer's solution. Fresh frozen plasma should be requested and, when available, 25 mL should be added to every 1 liter of lactated Ringer's solution.

3.Insertion of an intraventricular drain or catheter by a neurosurgeon and continuation of CSF irrigation with fluid removal through the lumbar access connected to a closed drainage system. Lactated Ringer's solution should be given by continuous infusion at 150 mL/hour, or at a rate of 75 mL/hour when fresh frozen plasma has been added as above.
The rate of infusion should be adjusted to maintain a spinal fluid protein level of 150 mg/dL.

PRECAUTIONS
General
Since the major route of excretion may be through the biliary system, toxicity from this drug may be increased when there is hepatic insufficiency.

If leukopenia with less than 2,000 white blood cells/mm^3 occurs following a dose of Vinblastine Sulfate, the patient should be watched carefully for evidence of infection until the white blood cell count has returned to a safe level.

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

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

Acute shortness of breath and severe bronchospasm have been reported following the administration of vinca alkaloids. These reactions have been encountered most frequently when the vinca alkaloid was used in combination with mitomycin-C and may require aggressive treatment, particularly 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 two weeks following a dose of mitomycin. Progressive dyspnea requiring chronic therapy may occur. Vinblastine should not be re-administered.

Care should be recommended in patients with ischemic cardiac disease.

The use of small amounts of Vinblastine Sulfate daily for long periods is not advised, even though the resulting total weekly dosage may be similar to that recommended.

Care must be taken to avoid contamination of the eye with concentrations of Vinblastine Sulfate used clinically. If accidental contamination occurs, severe irritation (or, if the drug was delivered under pressure, even corneal ulceration) may result. The eye should be washed with water immediately and thoroughly.

Drug Interactions
The simultaneous oral or intravenous administration of phenytoin and antineoplastic chemotherapy combinations that included Vinblastine Sulfate has been reported to have reduced blood levels of the anticonvulsant and to have increased seizure activity. Dosage adjustment should be based on serial blood level monitoring. The contribution of Vinblastine Sulfate 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.Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP 3A subfamily, or in patients with hepatic dysfunction. Concurrent administration of Vinblastine Sulfate with an inhibitor of this metabolic pathway may cause an earlier onset and/or an increased severity of side effects. Enhanced toxicity has been reported in patients receiving concomitant erythromycin.

Usage in Pregnancy
Vinblastine Sulfate should be given to a pregnant woman only if clearly needed. It can cause fetal harm when administered to a pregnant woman.

Nursing Mothers
It is not known whether Vinblastine Sulfate is excreted in human milk. But because of potential for adverse reactions from Vinblastine Sulfate in nursing infantes, this drug can be recommended for nursing mothers considering risk-benefit ratio.

ADVERSE REACTIONS
In general, the incidence of adverse reactions attending the use of Vinblastine Sulfate appears to be related to the size of the dose employed. With the exception of epilation, leukopenia and neurologic side effects, adverse reactions generally have not persisted for longer than 24 hours. Neurologic side effects are not common; but when they do occur, they often last for more than 24 hours. Leukopenia, the most common adverse reaction, is usually the dose-limiting factor.
The most common adverse reactions of Vinblastine Sulfate are underlined:

Hematologic - Leukopenia (granulocytopenia), anemia, thrombocytopenia (myelosuppression).

Dermatologic - Alopecia is common. A single case of light sensitivity associated with this product has been reported.

Gastrointestinal - Constipation, anorexia, nausea, vomiting, abdominal pain, ileus, vesiculation of the mouth, pharyngitis, diarrhea, hemorrhagic enterocolitis, bleeding from an old peptic ulcer and rectal bleeding.

Neurologic - Numbness of digits (paresthesias), loss of deep tendon reflexes, peripheral neuritis, mental depression, headache, convulsions.
Treatment with vinca alkaloids has resulted rarely in both vestibular and auditory damage to the eighth cranial nerve. Manifestations include partial or total deafness which may be temporary or permanent, and difficulties with balance including dizziness, nystagmus and vertigo. Particular caution is warranted when Vinblastine Sulfate is used in combination with other agents known to be ototoxic such as the platinum-containing oncolytics.

Cardiovascular - Hypertension, other cardiac effects such as myocardial infarction, angina pectoris and transient abnormalities of ECG related to coronary ischemia have been reported very rarely. Cases of unexpected myocardial infarction and cerebrovascular accidents have occurred in patients undergoing combination chemotherapy with vinblastine, bleomycin and cisplatin. Raynaud's phenomenon has also been reported with this combination.

Miscellaneous - Malaise, bone pain, weakness, pain in tumor-containing tissue, dizziness, jaw pain, skin vesiculation, hypertension, Raynaud's phenomenon when patients are being treated with Vinblastine Sulfate in combination with bleomycin and cis-platinum for testicular cancer. When epilation develops, it frequently is not total; and, in some cases, hair regrows while maintenance therapy continues. Extravasation during intravenous injection may lead to cellulitis and phlebitis.

OVERDOSAGE
Side effects following the use of Vinblastine Sulfate are dose related. Therefore, following administration of more than the recommended dose, patients can be expected to experience these side effects in an exaggerated fashion. There is no specific antidote.

STORAGE CONDITIONS
Store the vial in original carton in refrigerator at 2°C to 8°C (36°F to 46°F) temperature. Protect from light. Retain the vial in original carton until time of use.

PRESENTATION AND PACKAGING
Velvin Injection: Each commercial box contains 1 vial of Vinblastine Sulfate 10 mg Injection.

Manufactured by-
BEACON® Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

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