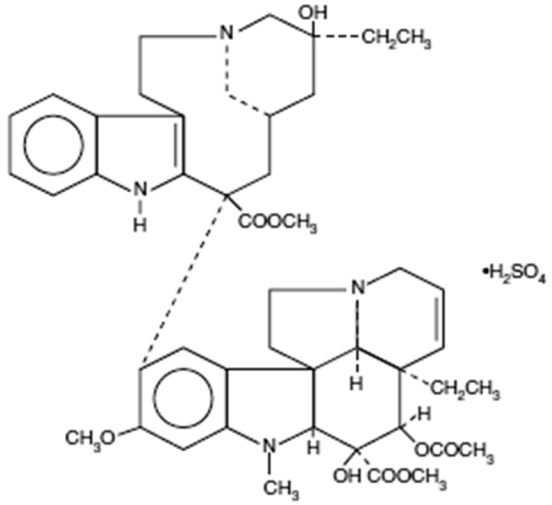
Z-BLASTIN (VINBLASTIN SULPHATE)

COMPOSITION

Each Vial Contains:
Vinblastin Sulphate IP equivalent to Vinblastin.....10mg

Description

Vinblastine Sulfate for Injection USP is vincaleukoblastine, sulfate (1:1) (salt). It is the salt of an alkaloid extracted from Vinca rosea Linn., a common fl owering herb known as the periwinkle (more properly known as Catharanthus roseus G. Don). Previously, the generic name was vincaleukoblastine, abbreviated VLB. It is a stathmokinetic oncolytic agent. When treated in vitro with this preparation, growing cells are arrested in metaphase. Chemical and physical evidence indicates that vinblastine sulfate has the molecular formula C46H58O9N4•H2SO4 and that it is a dimeric alkaloid containing both indole and dihydroindole moieties. The structural formula is as follows:



Vinblastine sulfate is a white to off-white powder. It is freely soluble in water, soluble in methanol, and slightly soluble in ethanol. It is insoluble in benzene, ether, and naphtha.

The clinical formulation is supplied in a sterile form for intravenous use only. Vials of Vinblastine Sulfate for Injection USP contain 10 mg (0.011 mmol) of vinblastine sulfate, in the form of a white, amorphous, solid lyophilized plug, without excipients. After reconstitution with sodium chloride solution, the pH of the resulting solution lies in the range of 3.5 to 5.

Pharmacodynamics

Experimental data indicate that the action of vinblastine sulfate is different from that of other recognized antineoplastic agents. Tissueculture studies suggest an interference with metabolic pathways of amino acids leading from glutamic acid to the citric acid cycle and to urea. In vivo experiments tend to confi rm the in vitro results. A number of in vitro and in vivo studies have demonstrated that vinblastine sulfate produces a stathmokinetic effect and various atypical mitotic fi gures. The therapeutic responses, however, are not fully explained by the cytologic changes, since these changes are sometimes observed clinically and experimentally in the absence of any oncolytic effects. Reversal of the antitumor effect of vinblastine sulfate by glutamic acid or tryptophan has been observed. In addition, glutamic acid and aspartic acid have protected mice from lethal doses of vinblastine sulfate. Aspartic acid was relatively ineffective in reversing the antitumor effect. Other studies indicate that vinblastine sulfate has an effect on cell-energy production required for mitosis and interferes with nucleic acid synthesis. The mechanism of action of vinblastine sulfate has been related to the inhibition of microtubule formation in the mitotic spindle, resulting in an arrest of dividing cells at the metaphase stage.

Pharmacokinetic

Pharmacokinetic studies in patients with cancer have shown a triphasic serum decay pattern following rapid intravenous injection. The initial, middle, and terminal half-lives are 3.7 minutes, 1.6 hours, and 24.8 hours, respectively. The volume of the central compartment is 70% of body weight, probably refl ecting very rapid tissue binding to formed elements of the blood. Extensive reversible tissue binding occurs. Low body stores are present at 48 and 72 hours after injection. Since the major route of excretion may be through the biliary system, toxicity from this drug may be increased when there is hepatic excretory insuffi ciency. The metabolism of vinca alkaloids has been shown to be mediated by hepatic cytochrome P450 isoenzymes in the CYP 3A subfamily. This metabolic pathway may be impaired in patients with hepatic dysfunction or who are taking concomitant potent inhibitors of these isoenzymes such as erythromycin. Enhanced toxicity has been reported in patients receiving concomitant erythromycin. (See PRECAUTIONS). Following injection of tritiated vinblastine in the human cancer patient, 10% of the radioactivity was found in the feces and 14% in the urine; the remaining activity was not accounted for. Similar studies in dogs demonstrated that, over 9 days, 30% to 36% of radioactivity was found in the bile and 12% to 17% in the urine. A similar study in the rat demonstrated that the highest concentrations of radioactivity were found in the lung, liver, spleen, and kidney 2 hours after injection.

Hematologic Effects: Clinically, leukopenia is an expected effect of vinblastine sulfate, and the level of the leukocyte count is an important guide to therapy with this drug. In general, the larger the dose employed, the more profound and longer lasting the leukopenia will be. The fact that the white-blood-cell count returns to normal levels after drug-induced leukopenia is an indication that the white-cell-producing mechanism is not permanently depressed. Usually, the white count has completely returned to normal after the virtual disappearance of white cells from the peripheral blood.

Following therapy with vinblastine sulfate, the nadir in white-blood-cell count may be expected to occur 5 to 10 days after the last day of drug administration. Recovery of the white blood count is fairly rapid thereafter and is usually complete within another 7 to 14 days. With the smaller doses employed for maintenance therapy, leukopenia may not be a problem.

Although the thrombocyte count ordinarily is not signifi cantly lowered by therapy with vinblastine sulfate, patients whose bone marrow has been recently impaired by prior therapy with radiation or with other oncolytic drugs may show thrombocytopenia (less than 200,000 platelets/mm3). When other chemotherapy or radiation has not been employed previously, thrombocyte reduction below the level 200,000/mm3 is rarely encountered, even when vinblastine sulfate may be causing signifi cant leukopenia. Rapid recovery from thrombocytopenia within a few days is the rule. The effect of vinblastine sulfate upon the red-cell count and hemoglobin is usually insignifi cant when other therapy does not complicate the picture. It should be remembered, however, that patients with malignant disease may exhibit anemia even in the absence of any therapy

INDICATIONS :

Vinblastine sulfate is indicated in the palliative treatment of the following:

I. Frequently Responsive Malignancies: Generalized Hodgkin's disease (Stages III and IV, Ann Arbor modifi cation of Rye staging system) Lymphocytic lymphoma (nodular 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)

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:

This preparation is for intravenous use only (see WARNINGS). Special Dispensing Information: WHEN DISPENSING VINBLASTINE SULFATE IN OTHER THAN THE ORIGINAL CONTAINER, IT IS IMPERATIVE THAT IT BE PACKAGED IN THE PROVIDED OVERWRAP WHICH BEARS THE FOLLOWING STATEMENT: "DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FOR

INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES." (see WARNINGS). A syringe containing a specifi c dose must be labeled, using the auxiliary sticker provided, to state: "FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES." Caution: 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 help disperse the drug and minimize discomfort and the possibility of cellulitis. There are variations in the depth of the leukopenic response which follows therapy with vinblastine sulfate. For this reason, it is recommended that the drug be given no more frequently than once every 7 days. Adult patients: It is wise to initiate therapy for adults by administering 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 sulfate. A simplifi ed and conservative incremental approach to dosage at weekly intervals for adults may be outlined as follows:

First dose ..... 3.7 mg/m2 bsa

Second dose ..... 5.5 mg/m2 bsa

Third dose ..... 7.4 mg/m2 bsa

Fourth dose ..... 9.25 mg/m2 bsa

Fifth dose ..... 11.1 mg/m2 bsa

The above-mentioned increases may be used until a maximum dose not exceeding 18.5 mg/m2 bsa for adults is reached. The dose should not be increased after that dose which reduces the white-cell count to approximately 3000 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 sulfate which will produce the above degree of leukopenia has been established, a dose of 1 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 sulfate should not be given until the white-cell count has returned to at least 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 the subsequent doses (See PRECAUTIONS). Pediatric Patients: A review of published literature from 1993 to 1995 showed that initial doses of vinblastine sulfate in pediatric patients varied depending on the schedule used and whether vinblastine sulfate was administered as a single agent or incorporated within a particular chemotherapeutic regimen. As a single agent for Letterer-Siwe disease (histiocytosis X), the initial dose of vinblastine sulfate was reported as 6.5 mg/m2. When

vinblastine sulfate was used in combination with other chemotherapeutic agents for the treatment of Hodgkin's disease, the initial dose was reported as 6 mg/m2. For testicular germ cell carcinomas, the initial dose of vinblastine sulfate was reported as 3 mg/m2 in a combination regimen. Dose modifi cations should be guided by hematologic tolerance. Patients with Renal or 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 modifi cation is recommended for patients with impaired renal function.

WARNINGS:

This product 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. Syringes containing this product should be labeled, using the auxiliary sticker provided to state ''FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES." Extemporaneously prepared syringes containing this product must be packaged in an overwrap which is labeled "DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES." After inadvertent intrathecal administration of vinca alkaloids, immediate neurosurgical intervention is required in order to prevent ascending paralysis leading to death. In a vey small number of patients, life-threatening paralysis and subsequent death was averted but resulted in devastating neurological sequelae, with limited recovery afterwards. There are no published cases of survival following intrathecal administration of vinblastine sulfate to base treatment on. However, based on the published management of survival cases involving the related vinca alkaloid vincristine sulfate, if vinblastine sulfate is mistakenly given by the intrathecal route, the following treatment should be initiated immediately after the injection.

PRECAUTIONS:

Toxicity may be enhanced in the presence of hepatic insufficiency. If leukopenia with less than 2,000 white blood cells/mm3 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 leukopenia 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.

ADVERSE REACTIONS

Prior to the use of the drug, patients should be advised of the possibility of untoward symptoms. 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 following are manifestations which have been reported as adverse reactions, in decreasing order of frequency. The most common adverse reactions 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, rectal bleeding.

Neurologic: Numbness of digits (paresthesias), loss of deep tendon refl exes, 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 diffi culties 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 platinum-containing oncolytics.

Cardiovascular: Hypertension. 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.

Drug Interactions:

Solutions should be made with normal saline (with or without preservative) and should not be combined in the same container with any other chemical. Unused portions of the remaining solutions that do not contain preservatives should be discarded immediately. 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.

OVERDOSAGE :

Signs and Symptoms: 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 effects in an exaggerated fashion.

CONTRAINDICATIONS:

Vinblastine sulfate is contraindicated in patients who have signifi cant 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.

STORAGE

This product should be refrigerated between 2°–8°C (36°–46°F). Discard unused solution. Protect from light. Store Upright.

PRESENTATION

Vinblastin Sulfate Injection, USP, preservative free solution.

10 mg/10 mL (single use)

Manufactured in India by:

ZUVIUS LIFESCIENCES PVT. LTD.
A WHO-GMP CERTIFIED COMPANY
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Link Road, Ghatkopar (East), Mumbai 400075.
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