WARNINGS

Caution: This preparation should be administered by individuals experienced in the administration of vinblastine sulfate. 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 a compression bandage are recommended to minimize discomfort and the possibility of cellulitis.

FATAL IF GIVEN INTRAThecALLY FOR INTRA- VENOUS USE ONLY

See WARNINGS for the treatment of patients given intrathecal vinblastine sulfate injection.

DESCRIPTION:

Vinblastine sulfate is the salt of an alkaloid extracted from Vinca rosea Linn., a common flowering herb known as the periwinkle (more properly known as Catharanthus roseus G. Don). Previously, the generic name was vincalukoblastine, 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 indicate that vinblastine sulfate is a dimeric alkaloid containing both indole and dihydroindole moieties. The accompanying structural formula has been proposed.

\[ \text{C}_{23}\text{H}_{29}\text{N}_{4}\text{O}_{6}\text{S}_{2} \]

Each mL contains: Vinblastine sulfate 1 mg; sodium chloride 9 mg; benzyl alcohol 0.9% (v/v) as a preservative; Water for Injection q.s. (pH 3.5 to 5.0).

CLINICAL PHARMACOLOGY:

Experimental data indicate that the action of vinblastine sulfate is different from that of other recognized anti-neoplastic agents. Tissue culture 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 confirm the in vitro results. A number of studies in vitro and in vivo have demonstrated that vinblastine sulfate produces a stathmokinetic effect and various atypical mitotic figures. The therapeutic responses, however, are not fully explained by the cytolytic changes, since these changes are sometimes observed clinically and experimentally in the absence of any oncotic 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 interference with nucleic acid synthesis. The mechanism of action of vinblastine 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 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 reflecting very rigid 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 impaired liver function. The route of excretion may be through the biliary system, toxicity from this drug may be increased when there is impaired liver function.

Clinical Toxicities of the Peripheral Nerve System

Approximately 25% of patients treated with vinblastine sulfate have complaints of paresthesias and paraesthesia. In some instances, these complaints may persist for weeks to months after discontinuation of the drug.

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 five to ten days after the last day of drug administration. Recovery of the white-cell 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 persist for weeks.

Although the thrombocyte count ordinarily is not significantly lowered by therapy with vinblastine sulfate, patients whose bone marrow has been recently impaired by prior therapy with radiation or with other oncologic drugs may show thrombocytopenia (less than 200,000 platelets/mm³). When other chemotherapy or radiation has not been employed previously, thrombocytopenia reduction below the level of 200,000/mm³ is rarely encountered, even when vinblastine sulfate may be causing significant 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 insignificant when other therapy does not also have a hematologic effect. As with leukopenia, however, that patients with malignant disease may exhibit anemia even in the absence of any therapy.

INDICATIONS AND USAGE:

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 differentiated)
- Histocytic 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

Current principles of chemotherapy for many types of cancer include the concurrent administration of several antineoplastic agents. For enhanced therapeutic effect without additive toxicity, agents with different dose-limiting clinical toxicities and different mechanisms of action are generally selected. Therefore, although vinblastine sulfate is effective as a single agent in the aforementioned indications, it is usually administered in combination with other antineoplastic drugs. Such combination therapy produces a greater percentage of responses than does a single-agent regimen. These principles have been applied, for example, in the chemotherapy of Hodgkin’s disease.

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 relapsed after treatment with the MOPP program—mechlorethamine hydrochloride (nitrogen mustard), vinblastine sulfate, prednisone and procarbazine—have likewise responded to combination-drug therapy that included vinblastine sulfate. A program 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 germ-cell cancers (embryonal carcinoma, teratocarcinoma and choriocarcinoma) are sensitive to systemic vinblastine alone, but better clinical results are achieved when vinblastine sulfate is administered concurrently 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.

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 any infection. This drug should not 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. Any person administering this product should be labeled, using the auxiliary sticker provided, to state “FATAL IF GIVEN INTRAThecALLY. FOR INTRaVEnOUS USE ONLY.”

Extemporaneously prepared syringes containing this product must be packaged in an overwrap which is labeled “DO NOT REMOVE COVERING UNtIL MOMENT OF INJECTION. FATAL IF GIVEN INTRAThecALLY FOR INTRA- VENOUS USE ONLY.”

After intravenous or other neoplastic administration of vinca alkaloids, immediate neurological intervention is required in order to prevent descending paralysis leading to death. In very small numbers of patients, life-threatening paralysis and subsequent death was averted but resulted in devastating neurologic sequelae, with limited recovery afterwards.
There are no published cases of survival following intrathelial administration of vinblastine sulfate to beateach other. However, based on the polydrug management of survival cases involving the related vinca alkaloid, it is possible that if vinblastine sulfate is mistakenly given by the intrathelial route, the patient should be observed immediately after injection:

1. Removal of as much CSF as is safely possible
2. Insertion of an epidural catheter into the subarachnoid space above the involved vertebrae
3. Any signs of irritation must occur, but if irritation is delayed, the patient should be observed for at least 2 hours after the injection. 
4. If irritation occurs, severe and persistent headache may occur, and that jaw pain and pain in the organs containing tumor tissue may occur. The latter is thought possible to result from swelling of tumor tissue during its response to treatment. Symptoms of its pretreatment extent will continue, and treatment with vinblastine sulfate will be delayed. 
5. Nausea and vomiting often occur, may last for up to 24 hours, and may persist for several days. 
6. Any other serious medical event should be reported to the physician.

Laboratory Tests

Since dose-limiting clinical toxicity is the result of depression of the white-blood-cell count, it is imperative that this count be obtained just before the planned dose of vinblastine sulfate. Since the duration of the effect is large compared to that of the drug itself, observation of the white-blood-cell count is the responsibility of the treating physician.

If the white-blood-cell count is below 5,000 per cubic millimeter, treatment should be delayed until the count has returned to normal. If the count is below 2,000 per cubic millimeter, treatment should be deferred until the count returns to normal. If no improvement occurs within 10 days, treatment should be stopped.

Liver enzymes should be determined at least once weekly during treatment, and if abnormalities develop, tests should be repeated at 5-day intervals. If abnormalities persist, the drug should be discontinued.

If the creatinine clearance is less than 0.8 ml per minute, vinblastine sulfate should be used with caution.

The rate of infusion should be adjusted to maintain a spinal fluid protein level of 150 mg/dL. If abnormal values have also been noted in addition but may not be essential:

(1) In cases of blurred vision, it may be given intranasally over 24 hours, followed by 50 mg three times daily, although not by mouth for 1 month. Folinic acid has also been administered intravenously as a 100 mg bolus and then infused at a rate of 25 mg/hour for 24 hours. Lactated Ringer's solution should be given intravenously at 150 mg/hour, or at a rate of 75 ml/hour when fresh frozen plasma has been administered.

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marmor should be considered life-threatening. The exact dose that will do this in all patients is unknown. Overdoses or reinfusions during prolonging consecutive-day infusions may be more toxic than the total dose given by rapid intravenous injection. The intravenous median lethal dose in mice is 10 mg/kg body weight; in rats, it is 2 g/kg. The oral median lethal dose in rats is 7 mg/kg.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastro-intestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying if the drug has been swallowed. Repeated doses of charcoal over time may have ten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

**DOSAGE AND ADMINISTRATION:**

This preparation is for intravenous use only (see WARNINGS).

Special Dispensing Information: WHEN DISPENSING VINBLASTINE SULFATE INJECTION IN OTHER THAN THE ORIGINAL CONTAINER, IT IS IMPERATIVE THAT IT BE PACKAGED IN THE PROVIDED OVERWRAP WHICH BEARS THE FOLLOWING STATEMENT: “DO NOT OPEN COVER UNTIL MOMENT OF INJECTION. FATAL IF GIVEN INTRATHECALLY FOR INTRAVENOUS USE ONLY” (see WARNINGS). A syringe containing a specific dose must be labeled with appropriate auxiliary stock to provide to state: “FATAL IF GIVEN INTRATHECALLY FOR INTRAVENOUS USE ONLY”.

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 will help disperse the drug and may minimize discomfort and the possibility of cell death.

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 seven days.

**Adult Patients**

It is wise to initiate therapy for adults by administering a single intravenous dose of 5.7 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 simplified 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** . . . . . . . . . . . . . . . . . . . . .9.2 mg/m² bsa
- **Fifth dose** . . . . . . . . . . . . . . . . . . . . .11.1 mg/m² bsa

The above-mentioned increases may be used until a maximum dose not exceeding 18.6 mg/m² bsa for adults is reached. The dose should not be increased after that dose which reduces the white-cell count to approximately 3,000 cells/mm³. In adults, 3.7 mg/m² bsa may produce this leukopenia; other adults may require more than 11 mg/m² bsa and, very rarely, as much as 18.5 mg/m² bsa may be necessary. For most adult patients, however, the white-cell count 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 further 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 and, if leukopenia is encountered, it is likely that 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 prolongated periods (ranging from 30 to 60 minutes or more), since this frequently results in irritation of the vein and increases the chance of extravasation.

Because of the enhanced possibility of thrombosis, it is considered advisable to inject the solution of vinblastine sulfate into an extremity in which the circulation is impaired or potentially impaired by such conditions as compressing vein, invading neoplasm, phlebitis or varicosity.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

**PRECAUTIONS**

**Intravenous Use Only.** In either case, the injection may be completed in one increment smaller than the above degree of leukopenia has been established, a further 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 and, if leukopenia is encountered, it is likely that the possibility of extravasation 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 prolongated periods (ranging from 30 to 60 minutes or more), since this frequently results in irritation of the vein and increases the chance of extravasation.

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**REFERENCES:**

6. National Study Commission on Cytotoxic Exposure—Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.

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