For the use only of a Registered Medical Practitioner / Oncologist or a Cancer Hospital or a Laboratory

Vincristine Sulfate for Injection USP 1mg

Rx Only
COMPOSITION

VINCRISTINE Lyo 1

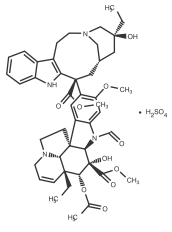
TAJ PHARMA

VINCRISTINE Lyo 1

Vincristine Sulfate for Injection USP 1mg
Each sterile lyophilized vial contains

Vincristine sulfate USP	1mg
Mannitol USP	100mg
Sodium Hydroxide USNF	q.s.
Sulfuric Acid USNF	q.s.

DESCRIPTION



Vincristine sulfate injection is the salt of an alkaloid obtained from a common flowering herb, the periwinkle plant *(Vinca rosea Linn)*. Originally known as leurocristine it has also been referred to as LCR and VCR. The molecular formula for Vincristine Sulfateis $C_{46}H_{56}N_2O_{10}$ H_2SO_4.It has a molecular weight of 923.04. Vincristine Sulfate for injection USP 1mg is a sterile lyophilized vial been added for pH adjustment.

CLINICAL PHARMACOLOGY

The mechanism of action of Vincristine Sulfate for injection has been related to the inhibition of microtubule formation in mitotic spindle, resulting in an arrest of dividing cells at the metaphase stage. Central nervous system leukemia has been reported in patients undergoing otherwise successful therapy with Vincristine Sulfate for injection. This suggests that Vincristine Sulfate for injection does not penetrate well into the cerebrospinal fluid. 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 5 minute, 2.3 hours, and 85 hours respectively; however, the range of the terminal half-life in humans is from 19 to 155 hours. The liver is the major excretory organ in humans and animals; about 80% of an injected dose of Vincristine Sulfate for injection appears in the feces and 10% to 20% can be found in the urine. Within 15 to 30 minutes after injection, over 90% of the drug is distributed from the blood into tissue, where it remains tightly, but not irreversibly, bound. Current principles of cancer chemotherapy involve the simultaneous use of several agents. Generally, each agent used has a unique toxicity and mechanism of action so that therapeutic enhancement occurs without additive toxicity. It is rarely possible to achieve equally good results with single-agent methods of treatment. Thus, Vincristine Sulfate for injection is often chosen as part of polychemotherapy because of lack of significant bone-marrow suppression (at recommended doses) and of unique clinical toxicity (neuropathy).

INDICATIONS

Vincristine Sulfate for injection is indicated in acute leukemia. Vincristine Sulfate for injection has also been shown to be useful in combination with other oncolytic agents in Hodgkin's disease, non-Hodgkin's malignant lymphomas (lymphocytic, mixed cell, histiocytic, undifferentiated, nodular and diffuse types), rhabdomyosarcoma, neuroblastoma, and Wilms' tumor.

CONTRAINDICATIONS

Patients with the demyelinating form of Charcot-Marie-Tooth syndrome would not be given Vincristine Sulfate for injection.

WARNINGS

This preparation is for intravenous use only. It should be administered by individuals experienced in the administration of Vincristine Sulfate for injection. The intrathecal administration of Vincristine Sulfate for injection usually results in death. Syringes containing 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 INTRAVENOUS USE ONLY." Treatment of patients following intrathecal administration of Vincristine Sulfate for injection has included immediate removal of spinal fluid and flushing with Lactated Ringer's, as well as other solutions and has not prevented ascending paralysis and death.

Pregnancy Teratogenic Effects

Pregnancy Category D.

Vincristine Sulfate for injection can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while receiving this drug, she should be appraised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

General - Acute uric acid nephropathy has been reported with Vincristine Sulfate for injection. In the presence of leukopenia or a complicating infection, administration of the next dose of Vincristine Sulfate for injection warrants careful consideration. If central nervous system leukemia is diagnosed, additional agents may be required, because Vincristine Sulfate for injection does not appear to cross the blood-brain barrier in adequate amounts.

Particular attention should be given to dosage and neurologic side effects if Vincristine Sulfate for injection is administered to patients with preexisting neuromuscular disease and when other drugs with neurotoxic potential are also being used.

Acute shortness of breath and severe broncospasm have been reported following the administration of Vincristine. These reactions are more frequent when the vinca alkaloid was used in combination with mitomycin-C and may require aggressive treatment, particularly when there is preexisting pulmonary dysfunction. The onset of these reactions may occur minutes to several hours after the vinca alkaloid is injected and may occur up to 2 weeks following the dose of mitomycin. Progressive dyspnea requiring chronic therapy may occur. Vincristine Sulfate should not be readministered.

Care must be taken to avoid contamination of the eye with concentration of Vincristine Sulfate for injection 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 immediately and thoroughly.

Laboratory Tests - Because dose-limiting clinical toxicity is manifested as neurotoxicity, clinical evaluation (e.g., history, physical examination) is necessary to detect the need for dosage modification. Following administration of Vincristine Sulfate for injection, some individuals may have a fall in the white blood cell count or platelet count, particularly when previous therapy or the disease itself has reduced bone-marrow function. Therefore, a complete blood count should be done before administration of each dose. Acute elevation of serum uric acid may also occur during induction of remission in acute leukemia; thus, such levels should be determined frequently during the first 3 to 4 weeks of treatment or appropriate measures taken to prevent uric acid nephropathy. The laboratory performing these tests should be consulted for its range of normal values.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Neither *in vivo* nor *in vitro* laboratory tests have conclusively demonstrated the mutagenicity of this product. Fertility following treatment with Vincristine Sulfate for injection alone for malignant disease has not been studied in humans.

Clinical reports of both male and female patients who received multiple-agent chemotherapy that included Vincristine Sulfate for injection indicate that azoospermia and amenorrhea can occur in postpubertal patients. Recovery occurred many months after completion of chemotherapy in some but not all patients. When the same treatment is administered to prepubertal patients, permanent azoospermia and amenorrhea are much less likely.

ADVERSE REACTIONS

In general, adverse reactions are reversible and are related to dosage. The most common adverse reaction is hair loss; the most troublesome adverse reactions are neuromuscular in origin. When single, weekly doses of the drug are employed, the adverse reactions of leukopenia, neuritic pain and constipation occur but are usually of short duration (i.e., less than 7 days). When the dosage is reduced, these reactions may lessen or disappear. The severity of such reactions seems to increase when the calculated amount of drug is given in divided doses. Other adverse reactions, such as hair loss, sensory loss, paresthesia, difficulty in walking, slapping gait, loss of deep-tendon reflexes and muscle wasting, may persist for at least as long as therapy is continued. Generalized sensorimotor dysfunction may become progressively more severe with continued treatment. Although most such symptoms usually disappear by about the 6th week after discontinuance of treatment, some neuromuscular difficulties may persist for prolonged periods in some patients. Regrowth of hair may occur while maintenance therapy continues. The following adverse reactions have been reported:

Hypersensitivity: Rare cases of allergic-type reactions, such as anaphylaxis, rash and edema that are temporally related to vincristine therapy.

Gastrointestinal: Constipation, abdominal cramps, weight loss, nausea, vomiting, oral, ulceration, diarrhea, paralytic ileus, intestinal necrosis and/or perforation and anorexia.

Genitourinary: Polyuria, dysuria and urinary retention due to bladder atony.

Cardiovascular: Hypertension and hypotension.

Neurologic: Sensory impairment, paresthesia , neuritic pain, motor difficulties ,loss of deep-tendon reflexes, foot drop, ataxia,paralysis ,cranial nerve manifestation, jaw pain, pharyngeal, parotid gland pain, bone pain, back pain, limb pain, myalgias, convulsions with hypertension, transient cortical blindness and optic atrophy with blindness.

Pulmonary: See PRECAUTIONS.

Endocrine: Inappropriate antidiuretic hormone secretion characterized by hyponatremia, renal or adrenal disease, hypotension, dehydration, azotemia.

Hematologic: Anemia, leukopenia, thrombocytopenia and thrombotopenia.

Skin: Alopecia and rash.

Other: Fever and headache.

DRUG INTERACTIONS

The simultaneous oral or intravenous administration of phenytoin and antineoplastic chemotherapy combinations that included Vincristine Sulfate for injection causes reduction in blood levels of the anticonvulsant and increases seizure activity. Dosage adjustment should be based on serial blood level monitoring. The contribution of Vincristine Sulfate for injection to this interaction is not certain. The interaction may result from reduced absorption of phenytoin and an increase in the rate of its metabolism and elimination.

DOSAGE AND ADMINISTRATION

This preparation is for intravenous use only. Neurotoxicity appears to be dose related. Extreme care must be used in calculating and administering the dose of Vincristine Sulfate for injection injection since overdosage may have a very serious or fatal outcome. SPECIAL DISPENSING INFORMATION: WHEN DISPENSING VINCRISTINE SULFATE FOR INJECTION IN OTHER THAN THE ORIGINAL CONTAINER, IT IS IMPERATIVE THAT IT BE PACKAGED IN AN OVERWRAP WHICH BEARS THE FOLLOWING STATEMENT. "DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY" (See WARNINGS). A syringe containing a specific dose must be labeled, using the auxiliary sticker provided, 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 vincristine is injected. Leakage into surrounding tissue during intravenous administration of Vincristine Sulfate for injection 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. Vincristine Sulfate for injection must be administered via an intact, free-flowing intravenous needle or catheter. Care should be taken that there is no leakage or swelling occurring during administration.

Preparation of Solution : Dissolve contents of the 1 mg vial in 1 mL of Sterile Water for Injection. If required the solution may be further diluted with 0.9% Sodium Chloride Injection or 0.5% dextrose injection. The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion. Injection of Vincristine Sulfate for injection should be accomplished within 1 minute.

The drug is administered intravenously at weekly intervals. The usual dose of Vincristine Sulfate for Injection for children is 1.5 mg/m^2-2 mg/m^2 For children weighing 10 kg or less, the starting dose should be 0.05 mg/kg, administered once a week. The usual dose of Vincristine Sulfate for injection for adults is 1.4 mg/m^2. A 50% reduction in the dose of Vincristine Sulfate for injection is recommended for patients having a direct serum bilirubin value above 3 mg/100 mL. Vincristine Sulfate for injection should not be given to patients while they are receiving radiation therapy through ports that include the liver. When Vincristine Sulfate for injection is used in combination with L-asparaginase, Vincristine Sulfate for injection should be given 12 to 24 hours before administration of the enzyme in order to minimize toxicity; administering L-asparaginase before Vincristine Sulfate for injection may reduce hepatic clearance of Vincristine.

Handling and Disposal

Handling and Disposal Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

OVERDOSE

Side effects following the use of Vincristine Sulfate for injection are dose related. In children under 13 years of age, death has occurred following doses of Vincristine Sulfate that were 10 times those recommended for therapy. Severe symptoms may occur in this patient group following dosages of 3 to 4 mg/m^2. Adults can be expected to experience severe symptoms after single doses of 3 mg/m^2 or more.

STORAGE

Store the vials in the original carton between 2°C and 8°C (36°F to 46°F). Protect from light.

SHELF LIFE

24 months

HOW SUPPLIED

VINCRISTINE Lyo 1

Vincristine Sulfate for Injection USP 1 mg
One lyophilized vial, individually packed in a carton

8 906096 627447

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Mfg. Lic. No: DD/L/809

Manufactured in India By:
TAJ PHARMACEUTICALS LIMITED
at SURVEY NO.188/1 TO 189/1,190/1 TO 4,
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