VINRACINE Injection

Vincristine sulfate 1 mg/1mL ; 2 mg/2 mL

COMPOSITION
VINRACINE INJECTION 1MG/1ML: Each vial contains :1 mg Vincristine Sulfate
VINRACINE INJECTION 2MG/2ML: Each vial contains :2 mg Vincristine Sulfate

PRODUCT DESCRIPTION
Colorless to pale yellow, clear solution in amber vials.

PHARMACODYNAMICS
Clinical Pharmacology
The mechanisms of action of VINRACINE remain under investigation. The mechanism of action of VINRACINE has been related to the inhibition of microtubule formation in the mitotic spindle, resulting in an arrest of diving cells at the metaphase stage. Central-nervous-system leukemia has been reported in patients undergoing otherwise successful therapy with VINRACINE. This suggests that VINRACINE does not penetrate well into the cerebrospinal fluid.
Pharmacokinetic studies in patients with cancer have shown a triphastic serum decay pattern following rapid intravenous injection. The initial, middle, and terminal half-lives are 5 minutes, 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 VINRACINE 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, VINRACINE is often chosen as part of polychemotherapy because of lack of significant bone-marrow suppression (at recommended doses) and of unique clinical toxicity (neuropathy).

Pharmacokinetics
Absorption : Vincristine sulfate is unpredictably absorbed from the GI tract. Following rapid N injection of a 2-mg dose of vincristine in patients with normal renal and hepatic function, peak serum drug concentrations of approximately 0.19-0.89 PM occur immediately and the drug is rapidly cleared from serum. The area under the serum vincristine concentration-time curve has been shown to be increased following continuous N infusion compared with rapid N injection of the drug when comparable doses are administered.
Distribution : Distribution of vincristine and its metabolites (and/or decomposition products) into human body tissues and fluids has not been fully characterized, but the drug is rapidly and apparently widely distributed following IV administration. Drug that is distributed into tissues is tightly but reversibly bound Vincristine and its metabolites (and/or decomposition products) are rapidly and extensively distributed into bile, with peak biliary concentrations occurring within 2-4 hours after rapid IV injection of the drug. Vincristine and its metabolites (and/or decomposition products) cross the blood-brain barrier poorly following rapid IV injection and generally do not appear in the CSF in cytotoxic concentrations. It is not known whether vincristine and its metabolites are distributed into mills.
Elimination : Following rapid IV injection of vincristine, serum concentrations of the drug appear to decline in a triphasic manner. The terminal elimination half-life of vincristine has ranged from 10.5-155 hours. The metabolic fate of vincristine has not been clearly determined; the drug appears to be extensively metabolized, probably in the liver, but the extent of metabolism is not clear since the drug also apparently undergoes decomposition in vivo. Vincristine and its metabolites (and/or decomposition products) are excreted principally in feces via biliary elimination. Following rapid IV injection in adults with normal renal and hepatic function, about 30% of a dose is excreted in feces within 24 hours and 70% within 72 hours; about 10% of a dose is excreted in urine within 24 hours, with very little urinary excretion occurring thereafter. The effects of hepatic impairment on the elimination of vincristine and its metabolites (and/or decomposition products) have not been evaluated, but individuals with decreased hepatic function may have impaired elimination

INDICATION
Vinracine (Vincristine Sulphate) is indicated in acute leukemia. Vincracine 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 Wilm`s tumor.

RECOMMANDED DOSE
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 VINRACINE, since overdosage may have a very serious or fatal outcome.
The concentration of VINRACINE is I mg/mL. Do not add extra fluid to the vial prior to removal of the dose. Withdraw the solution of VINRACINE into an accurate dry syringe, measuring the dose carefully. Do not add extra fluid to the vial in an attempt to empty it completely. The drug is administered intravenously at weekly intervals. The usual dose of VINRACINE for children is 2 mg/m2. For children weighing 10 kg or less, the starting dose should be 0.05mg/kg, administered once a week. The usual dose of VINRACINE for adult is 1.4 mg/m2 injection of VINRACINE should be accomplished within 1 minute.
1. Cautions
It is extremely important that the intravenous needle be properly positioned before vincristine is injected. Leakage into surrounding tissue during intravenous administration of VINRACINE my 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 hyluronidase 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. Whenever solution and container permit, parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.
2. Overdosage
Side effect following the use of VINRACINE is dose related. Extreme care must be used in calculating
and administration the dosed of VINRACINE since overdosage may have a very serious or fatal outcome. Do not exceed 2mg total once dose.
3. Therefore, following administration of doses higher than those recommended, patients can be expected experiencing exaggerated side effects.

SUPPORTIVE CARE SHOULD INCLUDE:
1) Prevention of side effects resulting from the syndrome of inappropriate secretion of antidiuretic
hormone. This includes restriction of fluid intake and perhaps the use of a diuretic affecting the function of Henie's loop and distal tubule.
2) Administration of an anticonvulsants.
3) Use of cathartics to prevent liens (in some instances, decompression of the gastrointestinal tract may be necessary).
4) Monitoring the cardiovascular system.
5) Determining daily blood counts for guidance in transfusion requirements.
Folic acid has been observed to have a protective effect in normal mice which were administered lethal
doses of vincristine. Isolated case reports suggest that folinic acid may be helpful in treating humans who have received an overdose.
It is suggested that 15mg of folinic acid be administered intravenously every 3 hours for 24 hours and then every 6 hours for at least 48 hours. Theoretically (Based on pharmacokinetic data), tissue levels of VINRACINE can be expected to remain significantly elevated for at least 72 hours. Treatment with folinic acid does not eliminate the need for the mentioned supportive measures.

MODE OF ADMINISTRATION
Injection

CONTRAINDICATION
Patients with the demyelinating form of Charcot-Marie-Tooth syndrome should not be given Vinracine. Carefully attention should be given to those conditions listed below and under Precautions and Warnings.

PATIENTS HYPERSENSITIVE TO VINCRISTINE/THE PRODUCT.
Patients with bone marrow insufficiency
Disorders of nervous system
Intrathecal administration.

PRECAUTIONS
Vincristine sulfate should be administered cautiously in the following patients.
1. Patients with liver impairment
2. Patients with renal dysfunction.
3. Patients with bone marrow suppression.
4. Patients with complicating infection.
5. Patients with a history of neuromuscular disease.
6. Patients with chickenpox. (Fatal systemic disorder may occur.)

GENERAL PRECAUTIONS
Acute uric acid nephropathy, which may occur alter the administration of oncolytic agents, has also been reported with VINRACINE. In the presence of leukopenia or a complicating infection, administration of the next dose of VINRACINE warrants careful consideration.

If central-nervous-system leukemia is diagnosed, additional agents may be required, because VINRACINE does not appear to cross the blood-brain barrier in adequate amounts.

Particular attention should be given to dosage and neurologic side effects if VINRACINE is administered to patients with preexisting neuromuscular disease and when other drugs with neurotoxic potential are also being used.
Care must be taken to avoid contamination of the eye with concentrations of VINRACINE 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 (eg : History, physical examination) is necessary to detect the need for dosage modification. Following administration of VINRACINE, 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 off 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 VINRACINE 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 VINRACINE indicate that azoospermia and amenorrhea can occur in postpubertal patients. Recovery occurred many months after completion of chemotherapy in some but not all patients.

The contributing role of VINRACINE in this development has not been determined. No evidence of carcinogenicity was found following intraperitoneal administration of VINRACINE in rats and mice, although this study was limited.

WARNINGS
This preparation is for intravenous use only. Individuals experienced in the administration of VINRACINE should administer it. Syringes containing this product should be labelled `WARNING - VINCRISTINE 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 VINRACINE has included immediate removal of spinal fluid and flushing with Lactated Ringer, as well as other solution and has not prevented ascending paralysis and death. In one case, progressive paralysis in an adult was arrested by the following treatment initiated immediately after the intrathecal injection:
1. As much spinal fluid was removed as could be safely done through lumbar access.
2. The subarachnoid space was flushed with Lactated Ringer's solution infused continuously through a catheter in a cerebral lateral ventricle at the rate of l50mL/h. The fluid was removed through a lumbar access.
3. As soon as fresh frozen plasma became available the fresh frozen plasma, 25 mL, diluted in 1L of
Lactated Ringer's solution was infused through the cerebral vertricular catheter at the rate of 75 mL/h with removal through the lumbar access.The rate of infusion was adjusted to maintain a protein level in the spinal fluid of 150 mg/dL.
4. Glutamic acid, 10g, was given intravenously over 24 hours followed by 500 mg 3 times daily by mouth for I month or until neurological dysfunction stabilized.
The role of glutamic acid in this treatment is not certain and may not be essential.

PEDIATRICS
Studies performed to date have not demonstrated pediatrics-specific problems that would limit the usefulness of vincristine in children.

GERIATRICS
Although appropriate studies with vincristine have not been performed in the geriatric population, elderly patients appear to be more susceptible to the neurotoxic effects.

CAUTIONS OF APPLICATION
1) This preparation is for intravenous use only. It should be administered by individuals experienced in the administration of VINRACINE. The intrathecal administration of VINRACINE usually results in death. Treatment of patients following intrathecal administration o VINRACINE ha 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. In one case, progressive paralysis in an adult was arrested by the following treatment initiated immediately after the intrathecal injection.
- As such spinal fluid was removed as could be safely done through lumbar access.
- The subarachinoid space was flushed with Lactated Ringer's solution infused continuously through a catheter in a cerebral lateral ventricle at the rate of 150mIJh. The fluid was removed through a lumbar access.
- As soon as fresh frozen plasma became available, the fresh frozen plasma, 25mL, diluted in 1L of Lactated Ringer's solution was infused through the cerebral ventricular catheter at the rate of 75mL/h with removal through the lumbar access. The rate of infusion was adjusted to maintain a protein level in the spinal fluid of 150mg/dL.
- Glutamic acid 10g, was given intravenously over 24 hours followed by 500mg 3 times daily by mouth for 1 month or until neurological dysfunction stabilized. The role of gutamic acid in this treatment is not certain and may not essential.
2) Leakage into surrounding tissue during intravenous administration of vincristine sulfate may cause necrosis and per vaginam in injection site. Therefore vincristine sulfate is administered cautiously.
3) Care must be taken to avoid contamination of the eye with concentrations of VINRACINE 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.

OTHERS
1) Neither in vivo nor in vitro laboratory tests have conclusively demonstrated the mutagenicity of this product. Fertility following treatment with VINRACINE 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 VINRACINE 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 had amenorrhea are much less likely. Patients who received chemotherapy with VINRACINE in combination with anticancer drugs known to be carcinogenic have developed second malignancies. The contributing role of VINRACINE in this development has not been determined. No evidence of carcinogenicity was found following intraperitoneal administration of VINRACINE in rats and mice although this study was limited.
2) If central nervous system leukemia is diagnosed, additional agents may be required, because
VINRACINE does not appear to cross the blood brain barrier in adequate amounts.
3) Chemotherapy combinations, which have included vincristine or vinca alkaloid single administration,
have been reported myocardial infarction and cerebral infarction.

CAUTIONS OF HANDLING
Vincristine sulfate should never be mixed with any other drug and should not be diluted in solutions that raise or lower the pH outside the range of 3.5 to 5.5. It should not be mixed with anything other than normal saline or glucose in water. After preparation, vincristine sulfate should be administered within a few hours.

INTERACTIONS WITH OTHER MEDICAMENTS
The simultaneous oral or intravenous administration of phenytoin and antineoplastic chemotherapy combinations that included vincristine sulfate has been repeated to reduce blood levels of the anticonvulsant and to increase seizure activity. Dosage adjustment should be based on serial blood level monitoring. The contribution of vincristine sulfate 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.

Acute shortness of breath and severe bronchospasm has 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 of these reactions may occur minutes to several hours after the vinca alkaloid in injected and may occur up to 2 weeks following the dose of mitomycin. Progressive dyspnea requiring chronic therapy may occur. Vinracine should not be readministered.

- Vincristine may raise the concentration of blood uric acid; dosage adjustment of antigout agents may be necessary to control hyperuricemia and gout; allopurinol may be preferred to prevent or reverse vincristine-induced hyper uicemia because if risk of uric acid neuropathy with uricosuric antigout agents such as probenecid and sulfinpyrasone.
- Concurrent use with asparaginase may result in additive neurotoxicity; if vincristine and asparaginase are to be used concurrently, toxicity appears to be less pronounced when asparaginase is administered after vincristine rather than before or with it.

- Concurrent use with doxorubicin and prednisolone may produce increased mylosuppression; it is recommended that he combination be avoided.
- Concurrent use with a live virus vaccine may potentate the replication of the vaccine virus, may increase the side adverse effects of the vaccine virus, and/or may decrease the patient's antibody response to the vaccine; immunization of these patients should be undertaken only with extreme caution after careful review of the patient's hematologic status and only with the knowledge and consent of the physician managing the vincristine therapy. Patients with leukemia in remission should not receive live virus vaccine until at least 3 months after their last chemotherapy. Immunization with oral poliovirus vaccine should also be postponed in persons in close contact with the patient, especially family members.

PREGNANCY AND LACTATION
Usage in Pregnancy
VINRACINE can cause fetal harm when administered to a pregnant woman. When pregnant mice and hamster were given doses of VINRACINE that caused the absorption 23% to 85% of fetuses, fetal malformations were produced in those that survived. Five monkeys were given single dose of VINRACINE between days 27 and 34 of their pregnancies, 3 of the fetuses were normal at term, and 2 viable fetuses had grossly evident malformations at term. In several animal species, VINRACINE can induce teratogenesis as well as embryo death that are nontoxic to the pregnant animal. There are no adequate and well control studies in pregnant woman. If this drug is used during pregnancy or if the patient

become pregnant while receiving this drug, she should be apprised of the potential hazard to the fetus. Woman of childbearing potential should be advised to avoid becoming pregnant.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions due to VINRACINE in nursing infants, a decision should be made either to discontinue nursing of the drug, taking into account the importance of the drug to the mother.

SIDE EFFECTS
Prior to the use of this drug patients and their parents guardian should be advised of the possibility of untoward symptoms. In general, adverse reactions and reversible and are related to dosage. The most common adverse reaction is alopecia: 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 (ie, 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 alopecia, 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, some neuromuscular difficulties may persist for prolonged periods in some patients. Re-growth 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 have been reported in patients receiving vincristine as apart of mufti drug chemotherapy regimes.
Gastrointestinal effect: Constipation, abdominal cramps, nausea, vomiting, oral ulceration, diarrhea, paralytic liens, intestinal necrosis and perforation, and anorexia have occurred. Constipation may take the form of upper colon impaction, and on physical examination, the rectum may be empty. Colicky abdominal pain coupled with an empty rectum may mislead the physician. A flat film of the abdomen is useful in demonstration this condition. All cases have responded to high enemas and laxatives. A routine prophylactic regimen against constipation is recommended for all patients receiving VINRACINE (Vincristine Sulfate).

Paralytic ileus (which mimics the 'surgical abdomen') may occur, particularly in young children. The ileus will reverse itself with temporary discontinuance of VINRACINE and with symptomatic care.

Genitourinary effect. Polyuria, dysuria and urinary retention due to bladder atony have occurred. Other drugs known to cause urinary retention (particularly in the elderly) should, if possible, be discontinued for the first few days following administration of VINRACINE.

Cardiovascular effect: Hypertension and hypotension have occurred. Chemotherapy combinations that have included vincristine sulfate, when given to patients previously treated with mediastinal radiation, have been associated with coronary artery disease and myocardial infarction. Causality has not been established.

Neurologic effect: Frequently, there is sequence to the development of neuromuscular side effects. Initially, only sensory impairment and paresthesia may be encountered. With continued treatment, neuritis pain and, later, motor difficulties may occur. There have been no reports made of any agent that can reverse the neuromuscular manifestations that may accompany therapy with VINRACINE. Loss of deep tendon reflexes, foot drop, ataxia, and paralysis have been reported with continued administration, cranial nerve manifestation including isolated paresis and paralysis of muscles controlled by cranial motor nerves may occur in absence of motor impairment elsewhere, extraocular and laryngeal muscles are those most commonly involved. Jaw pain, pharyngeal pain, parotid gland pain, bone pain, back pain, limb pain, and myalgias have been reported, pain in these areas may be severe. Convulsions, frequently with hypertension, have been reported in a few patients receiving VINRACIN. Several instances of convulsions followed by coma have been reported in children. Transient cortical blindness and optic atrophy with blindness have been reported.

Pulmonary: See Precautions.
Endocrine effect: Rare occurrences of a syndrome attributable to inappropriate antidiuretic hormone secretion have been observed in-patients treated with VINRACINE. The syndrome is characterized by high urinary sodium excretion in the presence of hyponatremia, renal or adrenal disease, hypotension, dehydration, azotemia, and clinical edema are absent. With fluid deprivation, improvement occurs in the hyponatremia and in the renal loss of sodium.

Hematologic effect: VINRACINE does not appear to have any constant or significant effect on platelets or red blood cells. Serious bone marrow depression is usually not a major dose-limiting event. However, anemia, leukopenia, and thrombocytopenia have been reported. Thrombocytopenia, if present when therapy with VINRACINE is begun, may actually improve before the appearance of marrow remission.

Skin- Alopecia and rash have been reported.

Others: Fever, headache, dyslogia, and weight reduction have occurred.

SYMPTOMS AND TREATMENT OF OVERDOSE
Side effects following the use of VINRACINE (Vincristine Sulfate) are dose related. In children under 13 years of age, death has occurred following doses of VINRACINE that were 10 times those recommended for therapy. Severe symptoms may occur in this patient group following dosages of 3 to 4 mg/m2. Adults can be expected to experience severe symptoms after single doses of 3 mg/m2 or more. Therefore, following administration of doses higher than those recommended, patients can be expected to experience exaggerated side effects. Supportive care should include the following: (1) prevention of side effects resulting from the syndrome of inappropriate antidiuretic hormone secretion (preventive treatment would include restriction of fluid intake and perhaps the administration of a diuretic affecting the function of Henle's loop and the distal tubule); (2) administration of anticonvulsants; (3) use of enemas or cathartics to prevent ileus (in some instances, decompression of the gastrointestinal tract may be necessary); (4) monitoring the cardiovascular system; and (5) determining daily blood counts for guidance in transfusion requirements.
Folinic acid has been observed to have a protective effect in normal mice that were administered lethal doses of Vinracine. Isolated case reports suggest that folinic acid may be helpful in treating humans who have received an overdosage of VINRACINE. It is suggested that 100 mg of folinic acid be administered intravenously every 3 hours for 24 hours and then every 6 hours for at least 48 hours. Theoretically (based on pharmacokinetic data), tissue levels of VINRACINE can be expected to remain significantly elevated for at least 72 hours. Treatment with folinic acid does not eliminate the need for the above-mentioned supportive measures.
Most of an intravenous dose of VINRACINE is excreted into the bile after rapid tissue binding. Because only very small amounts of the drug appear in dialysate, hemodialysis is not likely to be helpful in cases of overdosage. An increase in the severity of side effects may be experienced by patients with liver disease that is severe enough to decrease biliary excretion..
Enhanced fecal excretion of parenterally administered vincristine has been demonstrated in dogs pretreated with cholestyramine. There are no published clinical data on the use of cholestyramine as an antidote in humans.
There are no published clinical data on the consequence of oral ingestion of vincristine. Should oral ingestion occur, the stomach should be evacuated. Evacuation should be followed by oral administration of activated charcoal and a cathartic.

STORAGE CONDITION
Preserve in light-resistant, sealed containers. Store in a refrigerator (2°C to 8°C).
In-Use Storage Condition : Reconstituted solution is stable up to 8 hours, under normal light at 25°C.

Packaging available
1 mg/mL per vial X10'S per box ; 2 mg/2 mL per vial X10'S per box

Manufacturer
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