patients following intrathecal administration of vincristine sulfate has included immediate and permanent 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:

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 cerebellar lateral ventricle at the rate of 150 mL/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 1 L of Lactated Ringer’s solution was infused through the cerebellar ventricular 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, 10 g, was given intravenously over 24 hours followed by 500 mg 3 times daily by mouth for 1 month or until neurological dysfunction stabilized. The role of glutamic acid in this treatment is not certain and may not be essential.

Pregnancy Category D—Vincristine sulfate can cause fetal harm when administered to a pregnant woman. When pregnant mice and hamsters were given doses of vincristine sulfate that caused the resorption of 25% to 85% of fetuses, fetal malformations were produced in those that survived. Five monkeys were given single doses of vincristine sulfate between days 27 and 34 of their pregnancies; 3 of the fetuses were normal at term, and 2 viable fetuses had grossly evident neurologic damage at term. In several animal species, vincristine sulfate can cause azoospermia as well as embryo death at doses that are nontoxic to the pregnant animal. 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 apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

General—Acute uric acid nephropathy, which may occur after the administration of oncolytic agents, has also been reported with vincristine sulfate. In the presence of leukopenia or a complicating infection, administration of the next dose of vincristine sulfate warrants careful consideration.

If central nervous system leukemia is diagnosed, additional agents may be required because vincristine sulfate 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 is administered to patients with preexisting neuro muscular disease and when other drugs with neurotoxic potential are also being used.

Acute shortness of breath and severe bronchospasm have been reported following the administration of vincristine. These reactions have been encountered most frequently when the vincristine 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 vincristine is injected and may occur up to 2 weeks following the diagnosis of leukemia. Progressive dyspnea requiring chronic therapy may occur. Vincristine sulfate should not be readministered.

Care must be taken to avoid contamination of the eye with concentrations of vincristine 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 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 vincristine sulfate, some patients 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 1 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.

Drug Interaction—The simultaneous oral or intravenous administration of phenytoin and anticonvulsant chemotherapeutic combinations that included vincristine sulfate has been reported 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.

Carcinogenesis, Mutagenesis, Impairment Of Fertility—Neither in vivo nor in vitro laboratory tests have conclusively demonstrated the mutagenic potential of this product. Following treatment with vincristine sulfate 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 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 have been infrequent.

Patients who received chemotherapy with vincristine sulfate in combination with anticancer drugs known to be carcinogenic have developed second malignancies. The contributing role of vincristine sulfate in this development has not been determined. No evidence of carcinogenicity was found following intraperitoneal administration of vincristine sulfate in rats and mice, although this study was limited.

Usage In Pregnancy—Pregnancy Category D. See WARNINGS.
DOSAGE AND ADMINISTRATION

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

Neurotoxicity appears to be dose related. Extreme care must be used in calculating and administering the dose of vincristine sulfate, since overdosage may have a very serious or fatal outcome.

The concentration of vincristine contained in all vials of Vincristine Sulfate Injection, USP is 1 mg/mL. Do not add extra fluid to the vial prior to removal of the dose. Withdraw the solution of vincristine sulfate into an accurate dry syringe, measuring the dose carefully. Do not add extra fluid to the vial in an attempt to empty it completely.

Caution—It is extremely important that the intravenous needle or catheter be properly positioned before any vincristine sulfate injection, usp is injected. Leakage into surrounding tissue during intravenous administration of vincristine 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 tissue damage.

Vincristine sulfate 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. (see WARNINGS).

The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion (see Drug Interactions below). Injection of vincristine sulfate should be accomplished within 1 minute.

The drug is administered intravenously at weekly intervals.

The usual dose of vincristine sulfate for pediatric patients is 2 mg/m². For pediatric patients 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 adults is 1.4 mg/m². A 50% reduction in the dose of vincristine sulfate is recommended for patients having a direct serum bilirubin value above 3 mg/100 mL.

Vincristine sulfate should not be given to patients while they are receiving radiation therapy through ports that include the liver. When vincristine sulfate is used in combination with L-asparaginase, vincristine sulfate should be given 12 to 24 hours before administration of the enzyme in order to minimize toxicity. Administering L-asparaginase before vincristine sulfate may reduce hepatic clearance of vincristine sulfate.

Drug Interactions—Vincristine sulfate 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.

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

Procedures for proper handling and disposal of antineoplastic drugs should be considered. Several guidelines on this subject have been published.1,7 There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Special Dispensing Information—WHEN DISPENSING VINCRI STINE IN OTHER THAN THAN THE ORIGINAL CONTAINER, IT IS IMPERATIVE THAT IT BE PACKAGED IN THE PROVIDED OVERWRAP WHICH BEARS THE FOLLOWING STATEMENT: "DO NOT REMOVE COVERING OR OUTER WRAP UNTIL MOMENT OF INJECTION. 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: "FARAL IF GIVEN INTRATHORALLY FOR INTRAVENOUS USE ONLY".

HOW SUPPLIED

Vincristine Sulfate Injection, USP is preserved free and is supplied as follows:

<table>
<thead>
<tr>
<th>NDC</th>
<th>Number</th>
<th>Vincristine Sulfate Injection Volume</th>
</tr>
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<tbody>
<tr>
<td>0703</td>
<td>4402-11</td>
<td>1 mg/mL</td>
</tr>
<tr>
<td>0703</td>
<td>4411-11</td>
<td>1 mL</td>
</tr>
</tbody>
</table>

This product should be refrigerated. Protect from light and retain in carton until time of use.

REFERENCES


Issued: July 1999

Gensia Sicor Pharmaceuticals, Inc.

Irving, CA 92618