Name of drug
Vincristine Sulfate.

Description
Vincristine Sulfate is the salt of an alkaloid obtained from the periwinkle plant Vinca rosea (Catharanthus roseus).

Vincristine Sulfate Injection is a sterile, hypertonic, preservative-free solution containing Vincristine Sulfate 1mg/mL and Mannitol in Water for Injections.

Structural Formula:

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\begin{align*}
\text{OH} & \quad \text{N} \quad \text{O} \quad \text{CH}_3 \\
\text{H} & \quad \text{C} \quad \text{O} \quad \text{CH}_3 \\
\text{H}_3\text{CO} & \quad \text{O} \quad \text{C} \quad \text{OCH}_3 \\
\end{align*}
\]

Molecular formula: \(C_{46}H_{56}N_4O_{10}H_2SO_4\)
Molecular weight: 923.1
CAS No.: 2068-78-2

Pharmacology

Class of drug:
Antineoplastic agent. Antimitotic.

Mechanism of Action:
The precise mechanism of action of vincristine sulfate remains under investigation. Vincristine appears to affect cell mitosis by interfering with microtubular proteins and causing an arrest of cell division during the metaphase. It is cell cycle phase specific.

Pharmacokinetics:
Distribution: After intravenous administration, vincristine is rapidly distributed to body tissues. Vincristine is extensively protein bound (75%) and is reported to be concentrated in blood platelets. Vincristine does not penetrate the central nervous system to any significant degree.
Metabolism and Excretion: Vincristine is extensively metabolised in the liver. The main route of elimination is via the bile into the faeces. About 80% of an injected dose of vincristine appears in the faeces and 10-20% is excreted in the urine.

Indications
Vincristine is used primarily in the treatment of acute leukaemia, usually as a component of various chemotherapeutic regimens. It has also been used as part of combination therapy in the treatment of Hodgkin’s disease, non-Hodgkin’s malignant lymphomas, rhabdomyosarcoma, neuroblastoma,
Wilm’s tumour, osteogenic sarcoma, mycosis fungoides, Ewing’s sarcoma, carcinoma of the uterine cervix, breast cancer, malignant melanoma, oat-cell carcinoma of the lung and gynaecological tumours of childhood.

Vincristine may be useful in patients with true idiopathic thrombocytopenic purpura resistant to the usual treatment, but is not recommended as primary treatment for this disorder.

Contra-indications
1. Known hypersensitivity to vinca alkaloids or mannitol.
2. The demyelinating form of Charcot-Marie-Tooth-Syndrome should not be given vincristine.
3. Patients receiving radiation therapy through ports that include the liver.

Precautions
Vincristine should be used only by physicians experienced in therapy with cytotoxic agents.

1. **Administration:** This preparation is for intravenous use only. Vincristine is an irritant and should not be given intramuscularly, subcutaneously or intrathecally. Intrathecal administration of vincristine is usually fatal. When dispensed, syringes and vials containing this product should be labelled: **FOR INTRAVENOUS USE ONLY. FATAL IF GIVEN BY ANY OTHER ROUTE.**

Treatment of patients following accidental intrathecal administration of vincristine has included immediate removal of spinal fluid and flushing with Lactated Ringer’s solution, as well as other solutions but this 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:

a) As much spinal fluid was removed as could be safely done through lumbar access.
b) The subarachnoid space was flushed with Lactated Ringer’s solution infused continuously through a catheter in a cerebral lateral ventricle at the rate of 150mL/h. The fluid was removed through a lumbar access.
c) 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.
d) Glutamic acid, 10g was given intravenously over 24 hours followed by 500mg 3 times daily by mouth for 1 month or until neurological dysfunction stabilised. The role of glutamic acid in this treatment is not certain and may not be essential.

2. **Extravasation:** Vincristine is a vesicant and may cause a severe local reaction on extravasation. If leakage into the surrounding tissue occurs, the injection should be discontinued immediately and any remaining portion of the dose should be introduced into another vein. Local injection of hyaluronidase with the application of moderate heat has been used to disperse the drug and minimise discomfort and tissue damage.

3. **Nephrotoxicity:** Acute uric acid nephropathy has been reported with vincristine. The risk/benefit should be considered in patients with a history of gout or urate renal stones.
4. Vincristine penetrates the blood-brain barrier poorly, so alternate chemotherapeutic agents or routes of administration may be required for central nervous system leukaemia.
5. **Neurotoxicity:** Neurologic side effects of vincristine may be increased with the concomitant use of other neurotoxic agents, neuromuscular disease, in the elderly or patients who have had previous irradiation.
6. **Hepatic Impairment:** Impaired hepatic function or jaundice may warrant dosage adjustments, as vincristine is metabolised in the liver and excreted in the bile.
7. Avoid accidental contamination of the eyes, as vincristine is highly irritant and may cause corneal ulceration. The eyes should be washed with water immediately and thoroughly.

8. Although leucopenia is not common following therapy, both physician and patient should remain alert for signs of any complicating infection. Consideration should be given before administering further doses of vincristine if symptoms of a complicating infection arise.

9. Respiratory distress syndrome has been reported following the administration of vinca alkaloids in combination with Mitomycin-C. The onset of dyspnoea may occur minutes to several hours after the vinca alkaloid is administered, and may occur up to two weeks following the dose of Mitomycin-C. Progressive dyspnoea requiring chronic therapy may occur. Vincristine therapy should be discontinued.

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

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 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 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.

Use in pregnancy: Category D. Vincristine can cause foetal harm when administered to a pregnant woman. In several animal species vincristine is embryotoxic and teratogenic with doses that are non-toxic 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 advised of the potential hazard to the foetus. Women of child-bearing potential should be advised to avoid becoming pregnant.

Use in Lactation: It is not known whether vincristine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions due to vincristine in breastfed infants, a decision should be made either to discontinue breastfeeding or the drug, taking into account the importance of the drug to the mother.

Interactions with other drugs
Allopurinol may increase the incidence of cytotoxic induced bone-marrow depression.

The neurotoxicity of vincristine may be additive with that of other drugs acting on the peripheral nervous system (e.g. asparaginase and isoniazid).

The concurrent use of doxorubicin with vincristine and prednisolone may produce increased myelosuppression; it is recommended that this combination be avoided.

Vincristine appears to increase the cellular uptake of methotrexate by malignant cells and this principle has been applied in high-dose methotrexate therapy. The clinical importance of this interaction is not known however. It has also been reported that a 2.5 fold increase of methotrexate levels in C.S.F. occurred when vincristine was given 23 hours after high dose methotrexate therapy was initiated. The effect lasted approximately 3 hours.

Due to decreased absorption of the antimicrobial agent, the antimicrobial effect of oral quinolones (ciprofloxacin, norfloxacin and ofloxacin) may be decreased by administration of vincristine.

Nifedipine decreases the clearance of vincristine.
The simultaneous oral or intravenous administration of phenytoin and antineoplastic chemotherapy combinations that included vincristine 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 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.

Because normal defence mechanisms may be suppressed by vincristine therapy, concurrent use with a live virus vaccine may potentiate the replication of the vaccine virus, may increase adverse effects of the vaccine virus, and/or may decrease the patient’s antibody response to the vaccine. The patient’s antibody response to killed virus vaccine may also be decreased. Immunisation of these patients should be undertaken only with extreme caution after careful review of the patient’s haematological status and only with the knowledge and consent of the physician managing vincristine therapy. The interval between discontinuation of medications that cause immune suppression and restoration of the patient’s ability to respond to the vaccine depends on many factors; estimates vary from 3 months to 1 year.

Although not studied in vitro or in vivo, voriconazole may increase the plasma concentrations of vinca alkaloids including vincristine sulfate and lead to neurotoxicity. Therefore, it is recommended that dose adjustment of vincristine sulfate be considered.

Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP 3A sub-family or in patients with hepatic dysfunction. Concurrent administration of vincristine sulfate with itraconazole (a known inhibitor of the same metabolic pathway) has been reported to cause an earlier onset and/or increased severity of neuromuscular side effects.

Concurrent administration of mitomycin with vincristine may increase the incidence of acute shortness of breath and severe bronchospasm (see Precautions).

Laboratory Tests: Because dose-limiting clinical toxicity is manifested as neurotoxicity, clinical evaluation (eg history, physical evaluation) is necessary to detect the need for dosage modification. Following administration of Vincristine Sulfate 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 leukaemia; 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.

Hepatocellular dysfunction has been noted in some patients treated with vincristine sulfate. It is therefore recommended that liver function tests be performed on initiation of vincristine therapy and at periodic intervals during therapy depending on the patients clinical state, dosage and concomitant therapy.

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.

1. Neuromuscular: Neurotoxicity is the most common dose-limiting side effect. The development of neuromuscular effects is generally sequential with initial sensory impairment and paraesthesiae. With further treatment neuritic pain may develop and, later, motor difficulties. There have been no reports of any agent that can reverse these neuromuscular manifestations. Exacerbation of pre-existing neurological disorders may occur. Convulsions, accompanied by hypertension have been
reported. Ataxia, loss of deep-tendon reflexes, foot drop, cranial nerve palsy, paralysis, jaw pain, pharyngeal pain, parotid gland pain, bone pain, back pain, limb pain, myalgias and numbness of the digits have been observed. Several instances of convulsions followed by coma have been reported in children. Transient cortical blindness and optic atrophy have been reported. Sympathetic neuropathy may occur. Discontinuation of treatment should be considered if neuromuscular effects continue to be a problem.

2. **Central Nervous System:** Depression, agitation, insomnia, hallucinations and episodes of altered consciousness have been reported.

3. **Pulmonary:** see **Precautions**.

4. **Hypersensitivity:** Rare cases of allergic-type reactions, such as anaphylaxis, rash and oedema, that are temporally related to vincristine therapy have been reported in patients receiving vincristine as part of multidrug chemotherapy regimens.

5. **Haematologic:** With normal doses, reports of leucopenia, anaemia and thrombocytopenia are occasionally reported.

6. **Gastrointestinal:** Constipation and paralytic ileus are not uncommon and are frequently associated with abdominal cramps. Stool softeners, mild laxatives and enemas may be helpful. A routine prophylactic regimen of laxative and enemas is usually recommended for patients receiving vincristine. 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 demonstrating this condition. All cases have responded to high enemas and laxatives. Paralytic ileus (which mimics the ‘surgical abdomen’) may occur, particularly in young children and the elderly. The ileus will reverse itself with temporary discontinuance of vincristine and with symptomatic care. Nausea, vomiting, diarrhoea, anorexia, stomatitis, oral ulceration and intestinal necrosis and/or perforation occasionally occur.

7. **Genito-urinary:** Hyperuricaemia may occur in some patients receiving vincristine, especially those with non-Hodgkin’s lymphomas or leukaemia. In some patients uric acid nephropathy may result. These effects may be minimised by adequate hydration, alkalinisation of the urine and/or administration of allopurinol (see interactions with other drugs). Polyuria, dysuria and urinary retention due to bladder atony have occurred.

8. **Dermatological:** Alopecia is the most common adverse effect associated with vincristine therapy, occurring in 20-70% of patients. It is reversible upon discontinuation of the drug. Rash and photosensitivity reactions have also been reported.

9. **Endocrine:** Hypersecretion of antidiuretic hormone has been reported in patients receiving vincristine therapy. In these patients hyponatraemia associated with increased urinary sodium excretion occurs without evidence of renal or adrenal disease, hypotension, dehydration, azotaemia or clinical oedema. With fluid deprivation, improvement occurs in the hyponatraemia and in the renal loss of sodium.

10. **Cardiovascular:** Hypertension and hypotension have occurred. In patients previously treated with mediastinal radiation, coronary artery disease and myocardial infarction have been associated with chemotherapy combinations that have included vincristine. Causality has not been established.

11. **Other:** Fever and headache have occurred. Other side effects include defective sweating, myoclonic jerks, abnormal Valsalva response, impotence and diminished libido. Weight loss has been reported at high doses.
Dosage and administration
This preparation is for **intravenous use only** and is usually administered at **weekly intervals**.

Vincristine should not be given intramuscularly, subcutaneously or intrathecally. Intrathecal use of vincristine usually results in death. When dispensed, syringes and vials containing this product should be labelled: **FOR INTRAVENOUS USE ONLY. FATAL IF GIVEN BY ANY OTHER ROUTE.**

Vincristine Sulfate Injection may be injected into the tubing or sidearm of a free flowing I.V. infusion of 0.9% sodium chloride or 5% glucose, or directly into a vein over about one minute. Care should be taken to avoid extravasation. Vincristine Sulfate Injection 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 0.9% sodium chloride or 5% glucose.

Always check the needle position before injecting vincristine. If there is a swelling or other evidence of injection site leakage cease the injection/infusion and give the remaining dose at another site. Immediately apply local measures (hyaluronidase, local heat) to try to reduce both discomfort and the risk of cellulitis.

Vincristine has been given by many different dosing schemes and in combination with many other drugs. As the range between therapeutic and toxic levels is narrow and the response is varied, the dosage must always be carefully adjusted according to the needs of the individual.

**Children:**
- The usual dose is 1.5-2.0mg/m² body surface area.
- For children <10kg or body surface area <1m² 0.05mg/kg weekly.

**Adults:**
- The usual dose is 0.4-1.4mg/m² body surface area.

**Conditions Requiring Dosage Adjustment:**
- Patients with biliary obstruction; pre-existing neuropathies; liver dysfunction or jaundice; and the elderly.
- A direct serum bilirubin >3mg/100mL should prompt a 50% reduction in dosage.
- When used in combination with L-asparaginase, vincristine sulfate should be given 12 to 24 hours before the administration of the enzyme in order to minimise toxicity (see **Interactions with other drugs**); administering L-asparaginase before vincristine may reduce hepatic clearance of vincristine sulfate.

**Overdosage**
Overdosage with vincristine produces reactions that are mainly extensions of the adverse effects, as these are dose related. The treatment of vincristine overdosage is purely supportive and symptomatic, as no antidote has yet been found.

Adults may experience severe symptoms after single doses of 3mg/m² or more. In children under 13 years death has occurred following doses ten times those recommended for therapy. Severe symptoms may occur in this patient group following dosages of 3 to 4mg/m².

Anticonvulsants such as phenobarbitone may be beneficial in controlling seizures. If profound neutropenia develops, surveillance for the presence of infection by culture, protective isolation and early treatment with antibiotics when infection is suspected, may be necessary. Fluid restriction and possibly the use of an appropriate diuretic may have to be instituted to prevent side effects resulting from hypersecretion of antidiuretic hormone. Enemas may be used to prevent ileus (in some cases decompression of the G.I. tract may be necessary). Routine monitoring of the cardiovascular system is also recommended together with daily blood counts as an indicator for transfusion requirements.
Isolated case reports suggest that folinic acid may be helpful in treating humans who have received an overdose of vincristine. A suggested schedule is to administer 15mg of folinic acid intravenously every 3 hours for 24 hours and then every 6 hours for at least 48 hours. Theoretical tissue levels of vincristine derived from pharmacokinetic data are predicted to remain significantly elevated for at least 72 hours. Treatment with folinic acid does not eliminate the need for supportive measures.

An increase in the severity of side effects may be experienced in patients with liver disease with diminished biliary excretion.

Enhanced faecal 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. Nor is there published clinical data on the consequences of oral ingestion of vincristine. Should oral ingestion occur the stomach should be evacuated, and activated charcoal administered orally as a cathartic.

Most of an intravenous dose of vincristine is excreted in the bile after rapid tissue binding. Because only very small amounts of the drug appear in dialysate, haemodialysis is not likely to be helpful in cases of overdosage.

Handling precautions
As with all antineoplastic agents, trained personnel should prepare Vincristine Sulfate Injection. This should be performed in a designated area (preferably a cytotoxic laminar flow cabinet). Protective gown, mask, gloves and appropriate eye protection should be worn when handling vincristine. Where solution accidentally contacts skin or mucosa, the affected area should be immediately washed thoroughly with soap and water. It is recommended that pregnant personnel not handle cytotoxic agents such as vincristine. Luer-Lock fitting syringes are recommended. Large bore needles are recommended to minimise pressure and possible formation of aerosols. Aerosols may also be reduced by using a venting needle during preparation.

Items used to prepare vincristine, or articles associated with body waste, should be disposed of by placing in a double sealed polythene bag and incinerating at 1100°C. When handling urine and faeces from patients receiving vincristine, protective clothing should be worn for up to 4-7 days respectively after therapy.

Spills and disposal
If spills occur, restrict access to the affected area. Wear two pairs of gloves (latex rubber), a respirator mask, a protective gown and safety glasses. Limit the spread of the spill by covering with a suitable material such as absorbent towel or adsorbent granules. Spills may also be treated with 5% sodium hydroxide. Collect up absorbent/adsorbent material and other debris from spill and place in a leak proof plastic container and label accordingly. Cytotoxic waste should be regarded as hazardous or toxic and clearly labelled ‘CYTOTOXIC WASTE FOR INCINERATION AT 1100°C’. Waste material should be incinerated at 1100°C for at least 1 second. Cleanse the remaining spill area with copious amounts of water.

Presentation
AUST R 10828  Vincristine Sulfate Injection 1mg in 1mL (sterile) Plastic Vial (5’s).
AUST R 48055  Vincristine Sulfate Injection 2mg in 2mL (sterile) Plastic Vial (5’s).
AUST R 48057* Vincristine Sulfate Injection 5mg in 5mL (sterile) Plastic Vial (5’s).
*(For Hospital Use Only)
Storage
Store between 2-8°C. Refrigerate, do not freeze. Protect from light. Single use only. Discard unused portion.
The expiry date (month/year) is stated on the package after EXP.

Poison schedule
Australia - S4.

Manufacturer
Pfizer (Perth) Pty Limited
ABN 32 051 824 956
15 Brodie Hall Drive,
Bentley WA 6102 Australia

Sponsor in Australia
Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
West Ryde NSW 2114

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