AUSTRALIAN PRODUCT INFORMATION – VINCRISTINE SULFATE INJECTION

1. NAME OF THE MEDICINE

Vincristine sulfate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vincristine Sulfate Injection contains 1 mg/mL of vincristine sulfate.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Solution for injection.

Vincristine Sulfate Injection is a sterile, hypertonic, preservative-free solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Dose and method of administration

This preparation is for intravenous use only and is usually administered at weekly intervals. It can be fatal if administered intrathecally (see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use).

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

Dosage

Neurotoxicity appears to be dose related. Extreme care must be used in calculating and administrating the dose of vincristine since overdosage may have very serious or fatal outcome (see section 4.9 Overdose).

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.

The calculated dose of the vincristine solution should be administered ONLY through a vein by intravenous infusion (IV) according to the treatment protocol and under constant supervision for signs of extravasation.

Children

The usual dose is 1.5-2.0mg/m^2 body surface area.

For children <10kg or body surface area <1m^2 0.05mg/kg weekly.

Adults

The usual dose is 0.4-1.4mg/m^2 body surface area.

Method of administration

The diluted Vincristine Sulfate Injection must be infused via a flexible plastic container (e.g. infusion bag) into a free flowing I.V. infusion of 0.9% sodium chloride or 5% glucose, or directly into an intravenous catheter/needle, whichever is more suitable for the patient (see section 6.2 Incompatibilities). It is recommended to administer the solution over 5 to 10 minutes after dilution in a 50 mL infusion bag (50 mL sodium chloride or other compatible diluent). After administration the vein must be flushed through thoroughly. Care should be taken to avoid extravasation as this may cause local ulceration. 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.

TO REDUCE THE POTENTIAL FOR FATAL MEDICATION ERRORS DUE TO INCORRECT ROUTE OF ADMINISTRATION, VINCRISTINE SULFATE INJECTION IS RECOMMENDED TO BE DILUTED IN A FLEXIBLE PLASTIC CONTAINER AND PROMINENTLY LABELED AS INDICATED **FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES** (see Sections 4.3 Contraindications and 4.4 Special warnings and precautions of use).

Always check the needle position before intravenously administering vincristine. If there is a swelling or other evidence of injection site leakage, it may cause considerable irritation. Cease the infusion immediately 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.

Syringes should not be used for Vincristine Sulfate Injection administration. Preparation must be by dilution in small volume intravenous bags (the ‘minibag’ technique), rather than in a syringe, to protect against accidental administration via a spinal route.

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.

Do not add extra fluid to the vial prior to removal of the dose. Withdraw the solution of vincristine sulfate into an accurate syringe, measuring the dose carefully. Do not add extra fluid to the vial in an attempt to empty it completely.

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.

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 section 4.5 Interactions with other medicines and other forms of interactions); administering L-asparaginase before vincristine may reduce hepatic clearance of vincristine sulfate.

4.3 Contraindications

Known hypersensitivity to vincristine sulfate, other vinca alkaloids or any of the excipients.

Intrathecal administration, as usually results in death (see section 4.4 Special warnings and precautions for use).

Patients with the demyelinating form of Charcot-Marie-Tooth syndrome.

Patients receiving radiation therapy through ports that include the liver.

4.4 Special warnings and precautions for use

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

Precautions for Administration

This preparation is for intravenous use only. Can be fatal if administered intrathecally (see sections 4.2 Dose and method of administration and 4.3 Contraindications).

Vincristine is an irritant and should not be given intramuscularly, subcutaneously or intrathecally. Intrathecal administration of vincristine is usually fatal.

When dispensed, flexible plastic containers containing this product should be labelled:

FOR INTRAVENOUS USE ONLY. FATAL IF GIVEN BY ANY OTHER ROUTE.

Emergency Treatment of Accidental Intrathecal Administration

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 150mL/dL.

d) Glutamic acid, 10g was given intravenously over 24 hours followed by 500mg three times daily by mouth for one month or until neurological dysfunction stabilised. The role of glutamic acid in this treatment is not certain and may not be essential.

Extravasation

Vincristine is a vesicant and may cause a severe local reaction on extravasation. If leakage into the surrounding tissue occurs, the infusion 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.

Neurotoxicity

Neurotoxicity is the most common dose-limiting side effect (see section 4.8 Adverse effects). 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. Discontinuation of treatment should be considered if neuromuscular effects continue to be a problem.

Neurologic side effects of vincristine may be increased with the concomitant use of other neurotoxic agents, patients with pre-existing neuromuscular disease, in the elderly or in patients who have had previous irradiation. Particular attention should be given to dosage and neurological side effects in these patients.

Haematological

Effective therapy with vincristine is less likely to be followed by granulocytopenia than is the case with vinblastine and other oncolytic agents. A study of the side effects of vincristine injection solution in all age groups reveals that it is usually neuromuscular rather than bone marrow toxicity that limits dosage. Leucopoenia is not common following therapy, however because of the possibility of granulocytopenia, both physician and patient should remain alert for signs of any complicating infection.

Although pre-existing granulocytopenia does not necessarily contraindicate the administration of vincristine, the appearance of granulocytopenia and/or a complicating infection during treatment warrants careful consideration before giving the next dose.

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 section 4.5 Interactions with other medicines and other forms of interactions).

Urate Nephrotoxicity

Acute urate nephropathy, which may occur after the administration of oncolytic agents, has been reported with vincristine. The risk/benefit should be considered in patients with a history of gout or urate renal stones.

Treatment of Central Nervous System Leukaemia

Vincristine penetrates the blood-brain barrier poorly, so alternate chemotherapeutic agents or routes of administration may be required for central nervous system leukaemia. **Vincristine must not be administered intrathecally.**

Alopecia

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.

Optic

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.

Respiratory

Acute shortness of breath, severe bronchospasm and respiratory distress syndrome 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 be serious when there is pre-existing pulmonary dysfunction. 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 and should not be re-administered.

Secondary Malignancies

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.

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.

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.

Infection

The risks and benefits should be considered before vincristine is administered to patients with an infection, due to its immunosuppressive effects. It should be administered with caution to patients with herpes zoster or with existing or recent chicken pox (including recent exposure), as there is a risk of severe generalised disease developing.

Immunisation

Immunisation of patients being treated with vincristine should only be undertaken with extreme caution (see section 4.5 Interactions with other medicines and other forms of interactions). People in close contact with the patient, especially family members, should postpone immunisation with oral polio vaccines.

Use in hepatic impairment

Impaired hepatic function or jaundice may warrant dosage adjustments, as vincristine is metabolised in the liver and excreted in the bile. An increase in the severity of side-effects may be experienced by patients with liver disease sufficient to decrease biliary excretion.

Use in renal impairment

No data available.

Use in the elderly

See section 4.4 Special warnings and precautions for use: Neurotoxicity; Gastrointestinal. See section 4.2 Dose and method of administration, Dosage adjustment.

Paediatric use

See section 4.4 Special warnings and precautions for use: Gastrointestinal.

Effects on laboratory tests

Because dose-limiting clinical toxicity is manifested as neurotoxicity, clinical evaluation (e.g. 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.

4.5 Interactions with other medicines and other forms of interactions

Anti-gout Agents

Allopurinol may increase the incidence of cytotoxic induced bone-marrow depression. The mechanism for this potentiation has not been fully classified.

Dosage adjustment of anti-gout agents (e.g., allopurinol, colchicine, probenecid or sulfinpyrazone) may be necessary to control hyperuricaemia and gout, since vincristine may raise the concentration of blood uric acid.

Drugs Acting on the Peripheral Nervous System

The neurotoxicity of vincristine may be additive with that of other drugs acting on the peripheral nervous system (e.g. asparaginase and isoniazid) (see section 4.2 Dose and method of administration).

Doxorubicin

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

Methotrexate

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.

Oral Quinolones

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

Nifedipine decreases the clearance of vincristine.

Phenytoin

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 of phenytoin, based on serial blood level monitoring, should be made when it is used in combination with vincristine. 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.

Vaccines

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.

Voriconazole

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.

CYP 3A4 Inhibitors/Inducers

Caution should be exercised in patients concurrently taking drugs known to inhibit/induce 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 or

fluconazole (known inhibitors of the same metabolic pathway) has been reported to cause an earlier onset and/or increased severity of neuromuscular side effects. Inducers like St. John's wort should be given cautiously.

Digoxin

Studies have shown that cancer chemotherapy and radiation therapy have resulted in decreased absorption of the digitalis glycosides digoxin and B-acetyldigoxin administered in tablet forms. Serial monitoring of digoxin blood levels before, during and after chemotherapy should be initiated so that any necessary dosage adjustment can be made.

Mitomycin

Concurrent administration of mitomycin with vincristine may increase the incidence of acute shortness of breath and severe bronchospasm (see section 4.4 Special warnings and precautions for use).

Ototoxic Drugs

Vincristine should be used with extreme caution with potentially ototoxic drugs such as the platinum-containing antineoplastic agents, as temporary or permanent hearing impairment has been reported in patients receiving vinca alkaloids (see section 4.8 Adverse effects (undesirable effects)).

Bleomycin

Thromboembolism or Raynaud's syndrome may occur if bleomycin is used with vinca alkaloids and other agents such as cisplatin or etoposide (see section 4.8 Adverse effects (undesirable effects)).

Radiation Therapy

When chemotherapy is being given in conjunction with radiation therapy the use of vincristine should be delayed until radiation therapy has been completed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females:

Women of childbearing potential should be advised to avoid becoming pregnant while receiving vincristine sulfate. Due to the potential for genotoxicity, teratogenicity, and embryo toxicity, female patients of reproductive potential are advised to use highly effective contraception during treatment and for at least 7 months following last dose of vincristine sulfate.

Due to the potential for genotoxicity, male patients with female partners of reproductive potential are advised to use highly effective contraception during treatment and for at least 4 months following the last dose of vincristine sulfate.

Effects on fertility

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 amenorrhoea can occur in post-pubertal patients. Recovery occurred many months after completion of chemotherapy in some, but not all, patients. When the same treatment is administered to pre-pubertal patients, permanent azoospermia and amenorrhoea are much less likely.

Based on these clinical reports, male and female fertility may be compromised. It is recommended to discuss fertility preservation with men and women prior to treatment.

Use in pregnancy – Pregnancy Category D

Vincristine can cause fetal 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 fetus.

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, the mother should be advised not to breast-feed while on vincristine sulfate therapy and for 1 month following last dose of treatment. Alternatively, discontinue treatment taking into account the importance of the drug to the mother..

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, adverse effects of vincristine sulfate (with unknown frequency) may include dizziness, visual disturbances and neuromuscular effects which could affect the ability to drive or use machines. See Section 4.8 Adverse effects (undesirable effects).

4.8 Adverse effects (undesirable effects)

In general, adverse reactions are reversible and are related to dosage and cumulative dosage. The use of small amounts of vincristine daily for long periods is not advised. 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 effects of leucopenia, neuritic pain, and constipation occur but are of short duration (ie. less than 7 to 10 days). When the dosage is reduced, these effects may lessen or disappear. The severity of such effects seems to increase when the calculated amount of vincristine is given in divided doses. Other adverse effects such as hair loss, sensory loss, paraesthesia, difficulty in walking, slapping gait, loss of deep-tendon reflexes and muscle wasting may persist for at least as long as therapy is continued. Generalised sensorimotor dysfunction may become progressively more severe with continued treatment. Although most such symptoms usually disappear by about the sixth 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 reported adverse reactions are listed below by system organ class and by frequency. Frequencies are defined as: very common (≥1/10; ≥10%), common (≥1/100 to <1/10; ≥1% to

<10%), uncommon (≥1/1,000 to <1/100; ≥0.1% to <1%), rare (≥1/10,000 to <1/1,000; ≥0.01% to <0.1%), very rare (<1/10,000; <0.01%), and frequency not known (cannot be estimated from the available data).

Table 1: Adverse Reactions Table

System Organ Class	Very Common	Common	Uncommon	Frequency not known
Blood and Lymphatic System Disorders	Thrombocytopenia[a], anaemia			Granulocytopenia, leucopoenia
Immune System Disorders				Anaphylactic reaction[b], angioedema[b]
Endocrine Disorders				Inappropriate antidiuretic hormone secretion[c]
Metabolism and Nutrition Disorders	Hyponatraemia, decreased appetite			Dehydration, hyperuricaemia
Psychiatric disorders				Depression, agitation, insomnia, hallucination, altered state of consciousness
Nervous System Disorders[d]	Peroneal nerve palsy[e], paraesthesia		Coma[p]	Paralysis, convulsion[f, p], cranial nerve palsies multiple[g], sensory loss, autonomic neuropathy, areflexia, neuralgia, salivary gland pain, nerve injury, nystagmus, ataxia, myoclonus, motor dysfunction, balance disorder, gait disturbance, hypoaesthesia, dizziness, headache
Eye Disorders				Blindness transient, optic atrophy[h]
Ear and Labyrinth Disorders				Deafness[i], vertigo
Cardiac Disorders				Myocardial infarction[j], coronary artery disease[j]
Vascular Disorders				Hypotension, hypertension
Respiratory, Thoracic and Mediastinal Disorders		Oropharyngeal pain		Acute respiratory distress syndrome, bronchospasm

System Organ Class	Very Common	Common	Uncommon	Frequency not known
Gastrointestinal Disorders	Constipation[k], abdominal pain, vomiting, nausea	Ileus paralytic[l], diarrhoea		Intestinal perforation, gastrointestinal necrosis, stomatitis, mouth ulceration
Hepatobiliary Disorders				Venoocclusive liver disease[m]
Skin and Subcutaneous Tissue Disorders	Alopecia			Rash[b], photosensitivity reaction, defective sweating
Musculoskeletal, Connective Tissue and Bone Disorders	Myalgia, bone pain	Pain in jaw		Muscle atrophy, pain in extremity, back pain
Renal and Urinary Disorders		Urinary retention[n]		Urate nephropathy, polyuria, dysuria, atonic urinary bladder
Reproductive system and breast disorders				Erectile dysfunction, decreased libido
General Disorders and Administration Site Conditions				Pyrexia, injection site reaction, abnormal Valsalva response
Investigations	Weight decreased[o]			

a. If thrombocytopenia is present when treatment begins, it may actually improve before the appearance of marrow remission.

b. Reported in patients receiving vincristine as part of a multi-drug chemotherapy regimen.

c. Manifested by high urinary sodium excretion in the presence of hyponatraemia, renal or adrenal disease, hypotension, and dehydration.

d. Often dose limiting.

e. Manifests as foot drop and slapping gait.

f. Frequently with hypertension.

g. Especially affecting the extra-ocular and laryngeal muscles.

h. With blindness.

i. Temporary or permanent.

j. Reported in association with chemotherapy combinations that included vincristine when given to patients previously treated with mediastinal radiation.

k. Constipation may take the form of upper colon impaction and the rectum may be found to be empty on physical examination.

l. Paralytic ileus may occur particularly in young children. The ileus will reverse itself upon temporary discontinuance of vincristine and with symptomatic care.

m. Especially in children

n. Other drugs known to cause urinary retention (particularly in the elderly) should, if possible, be discontinued for the first few days following administration of vincristine.

o. Reported at high doses

p. Several instances reported in children.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Overdosage with vincristine produces reactions that are mainly extensions of the adverse effects, as these are dose related. Therefore, following administration of doses higher than those recommended, patients can be expected to experience side effects in an exaggerated fashion. 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/m^2 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/m^2.

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 or cathartics 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Antineoplastic agent. Antimitotic.

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.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

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 intravenous dose of vincristine appears in the faeces and 10-20% is excreted in the urine.

5.3 Preclinical safety data

Genotoxicity

Neither *in vivo* nor *in vitro* laboratory tests have conclusively demonstrated the mutagenicity of this product. As a classic tubulin binder, the primary mode of action of vincristine is aneugenicity, but at higher doses and over prolonged dosing intervals, the expression of clastogenicity becomes a possibility.

Carcinogenicity

No evidence of carcinogenicity was found following intraperitoneal administration of vincristine in rats and mice, although this study was limited.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Sodium Hydroxide

Sulfuric Acid

Water for Injections

Refer to Section 2: QUALITATIVE AND QUANTITATIVE COMPOSITION

6.2 Incompatibilities

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. See section 4.2 Dose and method of administration: Method of administration.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date (month/year) is stated on the package after EXP.

6.4 Special precautions for storage

Store between 2-8°C. Refrigerate, do not freeze. Protect from light. Single use only. Discard unused portion.

6.5 Nature and contents of container

Vincristine Sulfate Injection 1mg in 1mL (sterile) Plastic Vial (5's).

Vincristine Sulfate Injection 2mg in 2mL (sterile) Plastic Vial (5's).

*Vincristine Sulfate Injection 5mg in 5mL (sterile) Plastic Vial (5's).

* For Hospital Use Only.

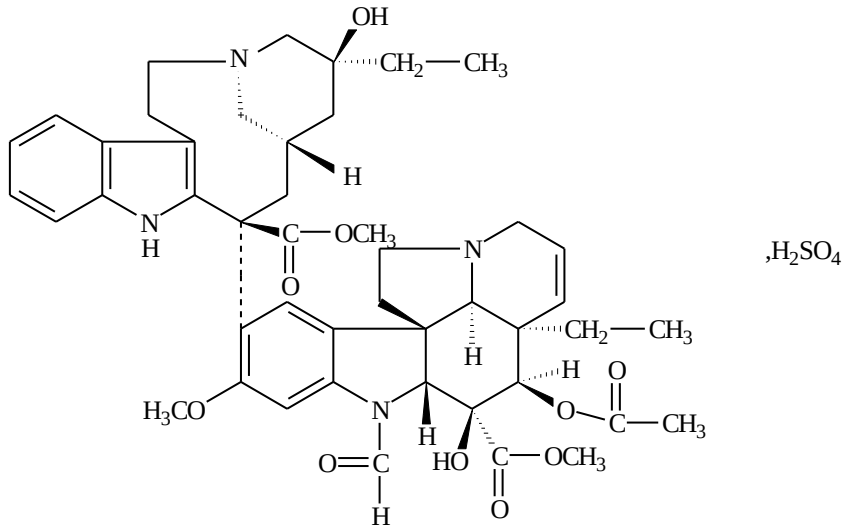
6.6 Special precautions for disposal

See section 4.2 Dose and method of administration: Handling precautions; Spills and disposal.

6.7 Physicochemical properties

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

Chemical structure



Molecular formula

$C_{46}H_{56}N_4O_{10},H_2SO_4$

Molecular weight

923.1

CAS number

2068-78-2

7. MEDICINE SCHEDULE (POISONS STANDARD)

(S4) Prescription Only Medicine.

8. SPONSOR

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9. DATE OF FIRST APPROVAL

9 July 1991

10. DATE OF REVISION

31 August 2023

Summary Table of Changes

Section changed	Summary of new information
4.2	Update to include further instructions on the administration of vincristine by intravenous infusion.
4.6	Update to information regarding use in Fertility, pregnancy and lactation.
5.3	Update to Pre-clinical safety data.