DBL® Vincristine Sulfate Injection

1. NAME OF THE MEDICINE

Vincristine sulfate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL® Vincristine Sulfate Injection:

1 mg/1 mL and 2 mg/2 mL injections contain vincristine sulfate 1 mg/mL and mannitol in Water for Injections. The solutions do not contain any preservative.

Vincristine sulfate occurs as a white or slightly yellow, hygroscopic, amorphous or crystalline powder and is freely soluble in water and slightly soluble in alcohol.

For the full list of excipients, see section **6.1 List of excipients**.

3. PHARMACEUTICAL FORM

Solution for injection.

DBL® Vincristine Sulfate Injection is a clear colourless solution. The solutions do not contain any preservative.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vincristine sulfate is indicated in acute leukaemia.

Current practices of cancer chemotherapy involve the simultaneous use of several agents. For enhanced therapeutic effect without additive toxicity, agents with different dose-limiting clinical toxicities and different mechanisms of action are generally selected. It is rarely possible to achieve equally good results with single agent treatment. Thus vincristine sulfate is often chosen as part of polychemotherapy because of lack of significant bone marrow suppression (at recommended doses) and because of its unique clinical toxicity (neuropathy). See section **4.2 Dose and method of administration** for possible increased toxicity when used in combination therapy.

It has 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, 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.

In recent years, multiple-agent regimens have been developed for the treatment of a variety of malignant disorders in children. Paediatric patients with neuroblastoma, osteogenic sarcoma, Ewing's sarcoma, rhabdomyosarcoma, Wilm's tumour, Hodgkin's disease, non-Hodgkin's lymphomas, embryonal carcinoma of the ovaries, and rhabdomyosarcoma of the uterus should be considered candidates for such polychemotherapy treatment. Close co-operation among oncologists, paediatricians, radiologists and surgeons is required in order to achieve the best possible results.

Patients with true idiopathic thrombocytopenic purpura refractory to splenectomy and short-term treatment with adrenocortical steroids may respond to vincristine sulfate, but the drug is not recommended as primary treatment for this disorder.

Recommended weekly doses of vincristine sulfate given for 3 to 4 weeks have produced permanent remissions in some patients. If patients fail to respond after 3 to 6 doses, it is unlikely that there will be any results with additional doses.

4.2 Dose and method of administration

Dosage

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.

Vincristine has been given by many different dosing schemes and in combination with many other medicines. Because of the narrow range between therapeutic and toxic levels and variations in response, the dosage must always be carefully adjusted according to the needs of the individual. Vincristine is usually administered at **weekly intervals.**

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

Children

The usual dose is 1.5 to 2.0 mg/m^2 body surface area (bsa).

For children weighing 10 kg or less, or having a bsa less than 1 m^2, the starting dose should be 0.05 mg/kg administered once a week.

Adults

The usual dose is 0.4 to 1.4 mg/m^2 bsa.

Elderly patients and those with underlying neurological disease may be more susceptible to the neurotoxic effects of vincristine. Dosage modification may also be required in patients with liver disease or jaundice. As stated under section **4.3 Contraindications**, vincristine should not be given to patients receiving radiation therapy through ports that include the liver. When used in combination with L-asparaginase, vincristine sulfate should be given 12 to 24 hours before 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.

Method of administration

This preparation is for intravenous use only (see Caution below) by individuals experienced in administration of vincristine sulfate. The intrathecal administration of vincristine sulfate is usually fatal.

DBL® Vincristine Sulfate Injection should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit.

The diluted DBL® Vincristine Sulfate Injection must be infused via a flexible plastic container (e.g., infusion bag) into a free-flowing intravenous 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 dextrose solution). After administration the vein must be

flushed through thoroughly. Care should be taken to avoid extravasation as this may cause local ulceration.

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 LABELLED AS INDICATED FOR **INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES** (see sections **4.3 Contraindications and 4.4 Special warnings and precautions for 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 DBL® Vincristine Sulfate Injection administration. Preparation must be by dilution in small volume intravenous bags (the 'minibag' technique), to protect against accidental administration via a spinal route.

Handling Precautions

As with all antineoplastic agents, trained personnel should prepare DBL® 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 sulfate. 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 sulfate.

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 DBL® Vincristine Sulfate Injection, or articles associated with body waste should be disposed of by placing in a double sealed polythene bag and incinerated at 1100°C.

When handling urine and faeces from patients receiving vincristine, protective clothing should be worn for up to 4 to 7 days respectively after therapy (see section **6.6 Special precautions for disposal**).

Dosage adjustment

A 50% reduction in the dose of vincristine sulfate is recommended for patients having a serum bilirubin value above 3 mg/100 mL for both children and adults.

4.3 Contraindications

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 should not be given vincristine sulfate.

Careful attention should be given to those conditions listed under section **4.4 Special warnings and precautions for use.**

DBL® Vincristine Sulfate Injection is contraindicated in patients who are hypersensitive to vincristine, vinca alkaloids or any other ingredient in the preparation.

Vincristine should not be administered to patients while they are receiving radiation therapy through ports that include the liver.

Vincristine should not be administered to women while they are breast-feeding (see section **4.6 Fertility, pregnancy and lactation**).

4.4 Special warnings and precautions for use

Vincristine should be used only by physicians experienced in cytotoxic chemotherapy.

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 very irritating 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 **"WARNING - FOR INTRAVENOUS USE ONLY - FATAL IF GIVEN BY OTHER ROUTES".**

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, 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 150 mL/hour. 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 cerebral ventricular catheter at the rate of 75 mL/hour 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 grams was given intravenously over 24 hours followed by 500 mg 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.

Extravasation

Vincristine is a vesicant and may cause a severe local reaction on extravasation. If leakage into the surrounding tissue should occur during intravenous administration of vincristine, 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 heat has been used to disperse the drug in order to minimise discomfort and the possibility of tissue damage.

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.

Urate nephrotoxicity

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

Treatment of central nervous system leukaemia

As vincristine penetrates the blood-brain barrier poorly, additional agents and routes of administration may be required for central nervous system leukaemia. **Vincristine must not be administered intrathecally.**

Neurotoxicity

Neurotoxicity is the most common dose-limiting side effect (see section **4.8 Adverse effects (undesirable effects**)). The development of neuromuscular effects is generally sequential with initial sensory impairment and paraesthesia. 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.

Particular attention should be given to dosage and neurologic side effects if vincristine is administered to patients who have had previous cytotoxic drug therapy or irradiation and in those with pre-existing neuromuscular disease (including sensory peripheral neuropathy and steroid-induced myopathy), and also when other drugs with neurotoxic potential are being used. The neurotoxic effect of vincristine may be additive with other neurotoxic agents or increased by spinal cord irradiation and neurological disease. Care should also be taken in elderly patients, who may be more susceptible to neurotoxicity (see section **4.2 Dose and method of administration**).

Respiratory

Acute shortness of breath and severe bronchospasm have 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 and may require aggressive treatment, particularly when there is pre-existing pulmonary dysfunction. The onset of these reactions may be within minutes or several hours after the vinca is administered and may occur up to 2 weeks following the dose of mitomycin. Progressive dyspnoea requiring chronic therapy may occur. Vincristine should not be readministered.

Secondary malignancies

Patients who received vincristine sulfate chemotherapy in combination with anticancer drugs known to be carcinogenic have developed secondary 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 in rats and mice, although this study was limited.

Optic

Care should be taken to avoid accidental contamination of the eyes, because vincristine is highly irritant and can cause corneal ulceration. The eyes should be washed with water immediately and thoroughly.

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

Because of the hepatic metabolism and biliary excretion of vincristine, a dosage reduction may be required in patients with liver disease or jaundice. 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 **4.2 Dose and method of administration**.

Paediatric use

See section **4.2 Dose and method of administration**.

Effects on laboratory tests

Because dose-limiting clinical toxicity is manifested as neurotoxicity, clinical evaluation (e.g., history, physical examination) is necessary to detect the need for dosage modification. Following administration of vincristine sulfate, 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 (see section **4.8 Adverse effects (undesirable effects)**). 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. Liver function tests are therefore recommended when vincristine therapy is initiated and at periodic intervals during therapy, depending on the patient's clinical state, the dosage used and any 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 asparaginase (see section **4.2 Dose and method of administration**), isoniazid and other medicines acting on the peripheral nervous system.

Doxorubicin

The concurrent use of doxorubicin with vincristine and prednisone may produce increased myelosuppression; it is recommended that the 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 cerebrospinal fluid (CSF) occurred when vincristine was given 23 hours after high dose methotrexate therapy was initiated. The effect lasted approximately 3 hours.

Vaccines

Because normal defence mechanisms may be suppressed by vincristine sulfate therapy, concurrent use with a live virus vaccine may potentiate the replication of the vaccine virus, and 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 may also be decreased. Immunisation of a patient who is receiving or who has received vincristine, should be undertaken only with extreme caution after careful review of the patient's haematologic status and only with the knowledge and consent of the physician managing the 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.

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.

Phenytoin

The simultaneous oral or intravenous administration of phenytoin and antineoplastic chemotherapy 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.

Nifedipine

Nifedipine decreases the clearance of vincristine.

CYP 3A4 inhibitors/inducers

Vincristine should be administered cautiously with drugs which inhibit or induce the cytochrome P450 isoenzyme CYP3A, as these drugs may decrease or increase vincristine metabolism, thereby increasing its toxicity. Concurrent administration with itraconazole or fluconazole (known inhibitors of this metabolic pathway) have been reported to cause an earlier onset and/or increased severity of neuromuscular side effects. This interaction is presumed to be related to inhibition of vincristine metabolism. Inducers like St. John's wort should be given cautiously.

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.

Digoxin

Cancer chemotherapy and radiation therapy may result 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.

Granulocyte-colony stimulating factors (G-CSFs)

G-CSFs such as filgrastim and pegfilgrastim should be administered at least 24 hours after receiving cytotoxic chemotherapy including vincristine sulfate, because of increased risk of myelosuppression.

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 sulfate for malignant disease has not been studied in humans. Clinical reports of both male and female patients who have 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 prepubertal 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 – Category D

Vincristine can cause fetal harm when administered to a pregnant woman. Vincristine sulfate can induce teratogenesis as well as embryo death 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 apprised 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 breast-fed 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)

Prior to the use of vincristine, patients and or parents/guardians should be advised of the possibility of untoward symptoms.

In general, adverse effects are reversible and are related to dosage. The most common adverse effect is hair loss; the most troublesome adverse effects are neuromuscular in origin. When single, weekly doses of the drug are employed, the adverse effects of leucopoenia, neuritic pain, and constipation occur but are of short duration (i.e., 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 following adverse effects have been reported:

Immune system disorders

Rare cases of allergic-type reactions, such as anaphylaxis, rash, oedema and angioedema, that are temporarily related to vincristine therapy have been reported in patients receiving vincristine as a part of multidrug chemotherapy regimens.

Gastrointestinal (GI) disorders

Autonomic toxicity such as 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.

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

Nausea, vomiting, diarrhoea, anorexia, stomatitis, oral ulceration, intestinal necrosis and/or perforation, abdominal cramps and abdominal distension occur occasionally.

Hepatobiliary disorders

Venoocclusive liver disease has been reported, especially in children.

Renal and urinary disorders

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**). Allopurinol may be preferred to minimise hyperuricaemia, because of the risk of uric acid nephropathy with uricosuric antigout agents.

Polyuria, oliguria, nocturia, dysuria, and urinary retention due to bladder atony have occurred. Other drugs known to have caused urinary retention (particularly in the elderly) should, if possible, be discontinued for the first few days following administration of vincristine sulfate. Increased urinary retention is especially likely to occur in elderly male patients with varying degrees of obstructive uropathy. Urinary incontinence has also been reported.

Cardiac and vascular disorders

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. Thromboembolism has been reported when bleomycin has been administered with vinca alkaloids and other agents such as cisplatin or etoposide; such combinations have also been implicated in producing Raynaud's syndrome.

Nervous system disorders

Neurotoxicity is the most common dose-limiting side effect of vincristine. Frequently, there is a sequence to the development of neuromuscular side effects. Initially, only sensory impairment and paraesthesia may be encountered. With continued treatment, neuritic 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 vincristine. Vincristine may exacerbate the signs and symptoms in patients with pre-existing neurological disorders. Consideration should be given to discontinuing treatment if neuromuscular effects continue to be a problem.

Loss of deep-tendon reflexes, foot drop, wrist drop, ataxia, and paralysis have been reported with continued administration. Cranial nerve manifestations, including isolated paresis and/or paralysis of muscles controlled by cranial motor nerves, may occur in the absence of motor impairment elsewhere; extra-ocular and laryngeal muscles are those most commonly involved. Numbness of the fingers and toes, atrophy, cramps, slapping gait, and difficulty in walking or inability to walk, may occur. Jaw pain, pharyngeal pain, salivary gland pain, bone pain, back pain, limb pain, testicular 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 vincristine sulfate. Several instances of convulsions followed by coma have been reported in children.

Sympathetic neuropathy may occur. Peripheral neuritis and neuralgia occur frequently.

Peroneal nerve palsy (manifesting as foot drop and slapping gait), areflexia, nerve injury have been reported.

Treatment with vinca alkaloids has resulted very rarely (<0.01%) in vestibular and auditory damage to the eighth cranial nerve. Manifestations include partial or total deafness, which may be permanent or temporary, and difficulties with balance including dizziness, nystagmus and vertigo. Vincristine should only be used concurrently with other potentially ototoxic drugs, such as the platinum-containing antineoplastic agents, with extreme caution.

Patients with existing neurological disorders such as poliomyelitis or Charcot-Marie-Tooth Syndrome may be at increased risk of neurotoxicity.

Psychiatric disorders

Depression, agitation, insomnia, hallucinations and altered state of consciousness have been reported.

Eye disorders

Transient cortical blindness and optic atrophy with blindness have been reported.

Respiratory, thoracic and mediastinal disorders

Oropharyngeal pain, acute respiratory distress syndrome and bronchospasm can occur (see section **4.4 Special warnings and precautions for use**).

Endocrine, metabolism and nutrition disorders

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) has occurred rarely 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. Decreased appetite is also very common.

Blood and lymphatic system disorders

Vincristine sulfate 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, anaemia, leucopoenia, and thrombocytopenia have been reported. Thrombocytopenia, if present when therapy with vincristine is begun, may actually improve before the appearance of bone marrow remission. Granulocytopenia can also occur.

Skin and subcutaneous tissue disorders

Alopecia is reported to occur in about 20% to 70% of patients who receive vincristine. It is reversible when vincristine is discontinued. Rash has also been reported, as have photosensitivity reactions.

Vincristine may cause a severe local reaction, resulting in pain and cellulitis, on extravasation (see section **4.4 Special warnings and precautions for use**).

Other

Fever and headache have occurred. Also other side effects include defective sweating, myoclonic jerks, abnormal Valsalva response, impotence and diminished libido. Weight loss has been reported at high doses.

4.9 Overdose

Signs and symptoms

Overdosage with vincristine produces adverse reactions that are mainly extensions of the common adverse effects as these are dose related. As no antidote for vincristine has been found to date, treatment is purely supportive and symptomatic.

In children under 13 years of age, death has occurred following doses of vincristine that were ten times those recommended for therapy. Severe symptoms may occur in this patient group following dosages of 3 to 4 mg/m^2. Adults can be expected to experience severe symptoms after single doses of 3 mg/m^2 or more (see section **4.8 Adverse effects (undesirable effects)**).

Treatment

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 GI tract may be necessary). Routine monitoring of the cardiovascular system is also recommended together with daily blood counts as an indicator for transfusion requirements.

Folinic acid has been observed to have a protective effect in normal mice which were administered lethal doses of vincristine sulfate. Isolated reports suggest that folinic acid may be helpful in treating humans who have received an overdose of vincristine. A suggested schedule is to administer 15 mg of folinic acid 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 vincristine 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 the intravenous dose of vincristine sulfate is excreted into the bile after rapid tissue binding (see section **5.2 Pharmacokinetic properties**). Because only very small amounts of the drug appear in dialysate, haemodialysis is not likely to be helpful in cases of overdosage. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

The precise mechanism of action of vincristine sulfate remains under investigation. It appears to bind to or crystallise critical microtubular proteins of the mitotic spindle, thus preventing their proper polymerisation and causing metaphase arrest. The antineoplastic effects of the vinca alkaloids are related to their ability to bind specifically with the intracellular protein tubulin, a key component of cellular microtubules.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Distribution

Distribution of vincristine and its metabolites into human body tissue and fluids has not been fully characterised, but the drug is rapidly and apparently widely distributed following intravenous administration.

Vincristine sulfate is extensively protein bound (75%) and is reported to be concentrated in blood platelets. Within 15 to 30 minutes after intravenous administration, over 90% of the drug is distributed from the blood into tissue, where it remains tightly, but not irreversibly, bound.

Vincristine sulfate and its metabolites are rapidly and extensively distributed into bile, with peak biliary concentrations occurring within 2 to 4 hours after rapid intravenous administration.

Central nervous system leukaemia has been reported in patients undergoing otherwise successful therapy with vincristine sulfate. This suggests that vincristine sulfate does not penetrate well into cerebro-spinal fluid.

Excretion

Pharmacokinetic studies in patients with cancer have shown a triphasic serum decay pattern following rapid intravenous administration. 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 intravenous dose of vincristine sulfate appears in the faeces and 10% to 20% can be found in the urine.

5.3 Preclinical safety data

Genotoxicity

Neither *in vivo* nor *in vitro* laboratory tests have conclusively demonstrated the mutagenicity of vincristine sulfate. 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

Patients who receive vincristine sulfate chemotherapy in combination with anticancer drugs known to be carcinogenic have developed secondary 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 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

6.2 Incompatibilities

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 0.9% sodium chloride injection or 5% glucose injection.

6.3 Shelf life

The expiry date can be found on the packaging.

After dilution

Chemical and physical in-use stability has been demonstrated for up to 24 hours at 2 - 8°C and at 25°C when Vincristine Sulfate Injection is diluted with 0.9% Sodium Chloride or 5% Dextrose in infusion bags and protected from light. If stored under normal light at 25°C, when diluted with 0.9% Sodium Chloride or 5% Dextrose, the diluted product is stable for 8 hours or 4 hours respectively.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at 2 to 8°C (Refrigerate. Do not freeze). Protect from light.

For storage conditions of the diluted medicinal product, see section **6.3 Shelf life**.

6.5 Nature and contents of container

DBL® Vincristine Sulfate Injection is a clear colourless solution and is available in the following presentations:

Strength	Container
1 mg Vincristine Sulfate /1 mL	2 mL vial
2 mg Vincristine Sulfate /2 mL	2 mL vial

Some product strengths or pack sizes may not be available in your country.

6.6 Special precautions for disposal

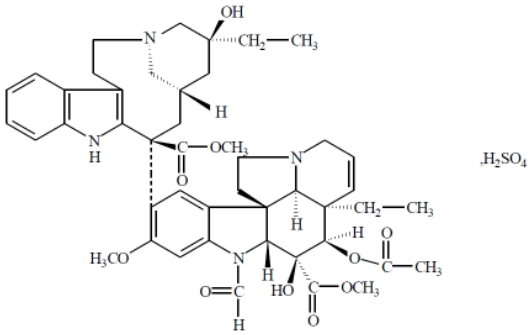
If spill occurs, restrict access to the affected area. Wear two pairs of latex rubber gloves, a suitable mask, a protective gown and safety glasses. Limit the spread of the spill by covering with a suitable material such as absorbent towels or adsorbent granules. Spills may also be treated with 5% sodium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

6.7 Physicochemical properties

Chemical structure

Vincristine sulfate, the salt of an alkaloid obtained from the periwinkle plant (*Catharanthus roseus*).

The chemical structure of Vincristine sulfate is shown below:



Molecular formula: is $C_{46}H_{56}N_4O_{10}$, H_2SO_4.

Molecular weight is 923.1.

The CAS registry number is 2068-78-2.

7. NAME AND ADDRESS OF MANUFACTURER

Hospira Australia Pty Ltd.
1 – 5, 7 – 23 and 25 – 39 Lexia Place
Mulgrave,
Victoria, 3170
Australia

Date of Revision: 25 FEB 2025