Name
Vincristine sulfate.

Description
Vincristine sulfate is the salt of an alkaloid obtained from the periwinkle plant (Cantharanthus roseus).

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.

DBL™ Vincristine Sulfate Injection:
A sterile solution of vincristine sulfate 1 milligram/mL and mannitol 100 milligrams/mL in Water for Injections. The solution does not contain any preservative.

Pharmacology
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.

Pharmacokinetics
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 injection, 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 injection.

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.

Pharmacokinetic studies in patients with cancer have shown a triphasic serum decay pattern following rapid intravenous injection. The initial, middle, and terminal half-lives are 5 minutes, 2.3 hours and 85 hours respectively; however the range of the terminal half-life in humans is from 19 to 155 hours. The liver is the major excretory organ in humans and animals; about 80% of an injected dose of vincristine sulfate appears in the faeces and 10% to 20% can be found in the urine.

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 Dosage and 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, Wilms'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.

**Contraindications**

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 **Precautions**.

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

Patients with known hypersensitivity to vinca alkaloids or mannitol should not be given vincristine sulfate.

**Use in pregnancy (Category D)**

Drugs which have caused, are suspected to have caused or may be expected to have caused, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Vincristine can cause foetal harm when administered to a pregnant woman. When pregnant mice and hamsters were given doses of vincristine sulfate that caused resorption of 23% to 85% of foetuses, foetal malformations were produced in those that survived. Five monkeys were given single doses of vincristine sulfate between days 27 and 34 of their pregnancies; 3 of the foetuses were normal at term, and 2 viable foetuses had grossly evident malformations at term. In several animal species, 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 foetus. Women of childbearing potential should be advised to avoid becoming pregnant.

**Precautions**

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

The drug is very irritating 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: **“WARNING – FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES”**

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 milligrams/dL.
4. Glutamic acid, 10 grams was given intravenously over 24 hours followed by 500 milligrams 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.
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 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 heat has been used to disperse the drug in order to minimise discomfort and the possibility of tissue damage.

Leucopenia is less likely following therapy with vincristine than is the case with other oncolytic agents. However, because of its possibility both physician and patient should remain alert for signs of any complicating infection. If leucopenia or a complicating infection is present, then administration of the next dose of vincristine warrants careful consideration.

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.

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.**

The neurotoxic effect of vincristine may be additive with other neurotoxic agents or increased by spinal cord irradiation and neurological disease.

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. Care should also be taken in elderly patients, who may be more susceptible to neurotoxicity (see Dosage and Administration).

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 occur up to 2 weeks following the dose of mitomycin. Progressive dyspnoea requiring chronic therapy may occur. Vincristine should not be readministered.

Because of the hepatic metabolism and biliary excretion of vincristine, a dosage modification may be required in patients with liver disease or jaundice.

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.

**Monitoring and laboratory tests**

Because dose-limiting clinical toxicity is manifested as neurotoxicity, clinical evaluation (eg. history, physical examination) is necessary to detect the need for dosage modification. Following administration of vincristine sulfate, some 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 above). The laboratory performing these tests should be consulted for its range of normal values.

**Interactions with other drugs**

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

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

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

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.

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.

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 decreases the clearance of vincristine.

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.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility
Neither in vivo nor in vitro laboratory tests have conclusively demonstrated the mutagenicity of vincristine sulfate. Fertility following the treatment of 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.

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

Adverse Reactions
Prior to the use of this drug, patients and or parents/guardians should be advised of the possibility of untoward symptoms.

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. When single, weekly doses of the drug are employed, the adverse reactions of leucopenia, neuritic pain, and constipation occur but are of short duration (ie. less than 7 days). When the dosage is reduced, these reactions may lessen or disappear. The severity of such reactions seems to increase when the calculated amount of drug is given in divided doses. Other adverse reactions such as 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 reactions have been reported:

**Hypersensitivity**

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

**Gastrointestinal**

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. The ileus will reverse itself with temporary discontinuance of vincristine and with symptomatic care. Nausea, vomiting, diarrhoea, stomatitis and oral ulceration occur occasionally.

**Genitourinary**

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, alkalisation of the urine and/or administration of allopurinol (see Drug interactions).

Polyuria, 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.

**Cardiovascular**

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

**Neurologic**

Frequently, there is a sequence to the development of neuromuscular side effects. Initially, only sensory impairment and paraesthesiae 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.

Loss of deep-tendon reflexes, foot 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. Jaw pain, pharyngeal pain, parotid gland pain, bone pain, back pain, limb pain, and myalgias have been reported; pain in these areas may be severe. Convulsions, frequently with hypertension, have been reported in a few patients receiving vincristine sulfate. Several instances of convulsions followed by coma have been reported in children. Transient cortical blindness and optic atrophy have been reported.

Depression, agitation, insomnia and hallucinations have been reported.

**Pulmonary**

See Precautions.

**Endocrine**

Hypersecretion of antidiuretic hormone (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.
Haematologic
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, leucopenia, and thrombocytopenia have been reported. Thrombocytopenia, if present when therapy with vincristine is begun, may actually improve before the appearance of bone marrow remission.

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

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

Dosage and 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.

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.

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

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

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.

Dosage
Vincristine has been given by many different dosing schemes and in combination with many other drugs. 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.

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.

Children
The usual dose is 1.5 to 2.0 milligrams/m² body surface area (bsa).
For children weighing 10 kg or less, or having a bsa less than 1 m², the starting dose should be 0.05 milligrams/kg administered once a week.

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

Adults
The usual dose is 0.4 to 1.4 milligrams/m² bsa.
A 50% reduction in the dose of vincristine sulfate is recommended for patients having a serum bilirubin value above 3 milligrams/100 mL.

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 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 **Interactions with other Drugs**); administering L-asparaginase before vincristine may reduce hepatic clearance of vincristine sulfate.

**DBL™ Vincristine Sulfate Injection** must be administered via an intact, free flowing intravenous catheter. Syringes should not be used for **DBL™ Vincristine Sulfate Injection** administration. Where possible, be prepared by dilution in small volume intravenous bags (the ‘minibag’ technique), rather than in a syringe, to protect against accidental administration via a spinal route. Care should be taken that there is no leakage or swelling occurring during administration (see **Precautions**).

**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 absorbent 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.

**Overdosage**

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 milligrams/m². Adults can be expected to experience severe symptoms after single doses of 3 milligrams/m² or more (see **Adverse Reactions**).

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 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 milligrams 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 **Pharmacology**). 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.

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

**Medicine Classification**
Prescription Medicine

**Presentation**

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**Date of Preparation**
25 May 2015