SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Vincristine Sulfate 1 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains 1 mg of vincristine sulfate
Each 2 ml contains 2 mg of vincristine sulfate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

A sterile, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vincristine sulfate is used either alone or in conjunction with other oncolytic drugs for the treatment of:

1. Leukaemias, including acute lymphocytic leukaemia, chronic lymphocytic leukaemia, acute myelogenous leukaemia and blastic crisis of chronic myelogenous leukaemia.

2. Malignant lymphomas, including Hodgkin's disease and non-Hodgkin's lymphomas.

3. Multiple myeloma.

4. Solid tumours, including breast carcinoma, small cell bronchogenic carcinoma, head and neck carcinoma and soft tissue sarcomas.

5. Paediatric solid tumours, including Ewing's sarcoma, embryonal rhabdomyosarcoma, neuroblastoma, Wilms' tumour, retinoblastoma and medulloblastoma.

6. Idiopathic thrombocytopenic purpura. Patients with true ITP refractory to splenectomy and short-term treatment with adrenocortical steroids may respond to vincristine sulfate but the medicinal product is not recommended as primary treatment of 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 beneficial results with additional doses.

4.2 Posology and method of administration

Posology

The following dosage regimens have been used:

Adults: The drug is administered intravenously at weekly intervals. The recommended dose is 1.4 to 1.5 mg/m^2 up to a maximum weekly dose of 2 mg.

Children: The suggested dose is 1.4 to 2 mg/m^2 given on a weekly basis with a maximum weekly dose of 2 mg. For children weighing 10 kg or less the starting dose should be 0.05 mg/kg administered as a weekly intravenous injection.

Elderly: The normal adult dose is still appropriate in the elderly.

Hepatic Impairment: Because of the hepatic metabolism and biliary excretion of vincristine sulfate, reduced doses are recommended in patients with obstructive jaundice or other hepatic impairment. Patients with liver disease sufficient to decrease biliary excretion may experience an increase in the severity of side-effects. A 50 per cent reduction in the dose of vincristine sulfate is recommended for patients having a direct serum bilirubin value above 3 mg/100 ml (51 micromol/l) (see section 4.4).

Method of administration

Precautions to be taken before handling or administering the medicinal product.

This preparation is for intravenous (IV) use only. It should only be administered by individuals experienced in vincristine administration.

FOR INTRAVENOUS USE ONLY

FATAL IF GIVEN BY ANY OTHER ROUTE

Can be fatal if administered intrathecally (see sections 4.3 and 4.4). See section 4.4 for use for the treatment of patients accidentally given intrathecal vincristine sulfate.

Vincristine sulfate is administered by intravenous infusion at weekly intervals.

Great care should be exercised in calculating and administering the dose, as overdosage may be extremely serious or even fatal. The calculated dose of the vincristine solution should be administered ONLY through a vein either by intravenous injection or infusion (IV) according to the treatment protocol and under constant supervision for signs of extravasation. The dose should not be increased beyond the level which produces therapeutic benefit. Individual doses should not exceed 2 mg; and white cell counts should be carried out before and after giving each dose.

Intravenous injection
Direct injection into the vein may be completed in about one minute.

Intravenous infusion
The diluted vincristine sulfate injection may be infused via a flexible plastic container (e.g.: infusion bag) either directly into an intravenous catheter/needle or into a running intravenous infusion (see section 6.2). It is recommended to administer the solution over 5 to 10 minutes after dilution in a 50 ml infusion bag (50 ml sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection). After administration the vein must be flushed through thoroughly. Care should be taken to avoid extravasation as this may cause local ulceration.
Caution: If leakage into surrounding tissue should occur during intravenous administration of vincristine sulfate, it may cause considerable irritation. The injection should be discontinued immediately and any remaining portion of the dose should then be introduced into another vein. Local injection of hyaluronidase and the application of moderate heat to the area of leakage help to disperse the drug and are thought to minimise discomfort and the possibility of cellulitis.

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

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 and 4.4).

Because of the narrow range between therapeutic and toxic levels and variations in response, the dosage must always be adjusted to the individual.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Intrathecal administration of vincristine sulfate is usually fatal (see section 4.4).

Hypersensitivity to vincristine sulfate or to any of the excipients listed in section 6.1.

Patients with the demyelinating form of Charcot-Marie-Tooth syndrome should not be given vincristine sulfate.

Careful notice should also be given to those conditions listed in section 4.4.

4.4 Special warnings and precautions for use

This preparation is for intravenous use only (see sections 4.2 and 4.3). Can be fatal if administered intrathecally.
It should be administered by physicians experienced in the administration of vincristine sulfate.
Vincristine sulfate should not be given by intrathecal, intramuscular or subcutaneous injection.

Syringes containing this product should be labelled ‘VINCRISTINE FOR INTRAVENOUS USE ONLY. FATAL IF GIVEN BY OTHER ROUTES’.

Emergency Treatment of accidental intrathecal administration:

After inadvertent intrathecal administration, immediate neurosurgical intervention is required in order to prevent ascending paralysis leading to death. In a very small number of patients, life-threatening paralysis and subsequent death was averted but resulted in devastating neurological sequelae, with limited recovery afterwards.

Based on the published management of these survival cases, if vincristine sulfate is mistakenly given by the intrathecal route, the following treatment should be initiated **immediately after the injection:**

1. Removal of as much cerebrospinal fluid (CSF) as is safely possible through the lumbar access.

2. Insertion of an epidural catheter into the subarachnoid space via the intervertebral space above initial lumbar access and CSF irrigation with lactated Ringer's solution. Fresh frozen plasma should be requested and, when available, 25 ml should be added to every 1 litre of lactated Ringer's solution.
3. Insertion of an intraventricular drain or catheter by a neurosurgeon and continuation of CSF irrigation with fluid removal through the lumbar access connected to a closed drainage system. Lactated Ringer's solution should be given by continuous infusion at 150 ml/h, or at a rate of 75 ml/h when fresh frozen plasma has been added as above.

The rate of infusion should be adjusted to maintain a spinal fluid protein level of 150 mg/dl.

The following measures have also been used in addition but may not be essential:

Folinic acid has been administered intravenously as a 100 mg bolus and then infused at a rate of 25 mg/h for 24 hours, then bolus doses of 25 mg 6-hourly for 1 week. Intravenous administration of glutamic acid 10 g over 24 hours, followed by 500 mg three times daily by mouth for one month. Pyridoxine has been given at a dose of 50 mg 8 hourly by intravenous infusion over 30 minutes. Their roles in the reduction of neurotoxicity are unclear.

Vincristine sulfate is a vesicant and may cause severe local reaction or extravasation, see *Caution* in section 4.2.

<u>Interaction with azole antifungals</u>
Concomitant administration of azole antifungals with vincristine has been associated with neurotoxicity and other serious adverse reactions, including seizures, peripheral neuropathy, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and paralytic ileus. Reserve azole antifungals for patients receiving vincristine who have no alternative antifungal treatment options (see section 4.5).

<u>Haematological</u>
Granulocytopenia is less likely following therapy with vincristine sulfate than is the case with other oncolytic agents. It is usually neuromuscular rather than bone marrow toxicity that limits dosage. However, because of the possibility of granulocytopenia, both physician and patient should remain alert for signs of any complicating infection. If granulocytopenia or a complicating infection is present, then administration of the next dose of vincristine sulfate warrants careful consideration. On occasions, these infections may prove fatal.

<u>Hepatic impairment</u>
An increase in the severity of side-effects may be experienced by patients with liver disease sufficient to decrease biliary excretion (see section 4.2).

<u>Urate nephropathy</u>
Acute uric acid nephropathy, which may occur after administration of oncolytic agents, has also been reported with vincristine sulfate.

<u>Neurological</u>

As vincristine sulfate penetrates the blood-brain barrier poorly, additional agents and routes of administration may be required for central nervous system leukaemias.

The neurotoxic effect of vincristine sulfate may be additive with other neurotoxic agents or increased by spinal cord irradiation and neurological disease. Elderly patients may be more susceptible to the neurotoxic effects of vincristine sulfate.

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-C (see section 4.5).

Mutagenicity
Both in vivo and in vitro laboratory tests have failed to demonstrate conclusively that this product is mutagenic. Fertility following treatment with vincristine sulfate alone for malignant disease has not been studied in humans. Clinical reports of both male and female patients who received multiple-agent chemotherapy that included vincristine sulfate indicate that azoospermia and 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, it is much less likely to cause permanent azoospermia and amenorrhoea.

Secondary malignancies
Patients who received 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 in rats and mice, although this study was limited.

Eyes disorders
Care should be exercised to avoid accidental contamination of the eyes as vincristine sulfate is highly irritant and can cause corneal ulceration. The eye should be washed immediately and thoroughly.

4.5 Interaction with other medicinal products and other forms of interaction

Isoniazid
The neurotoxicity of vincristine sulfate may be additive with that of isoniazid and other drugs acting on the nervous system.

Mitomycin-C
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-C and may be serious when there is pre-existing pulmonary dysfunction. The onset 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 sulfate should not be re-administered.

Phenytoin
The simultaneous oral or intravenous administration of phenytoin and antineoplastic chemotherapy combinations, that included vincristine sulfate, have been reported to reduce blood levels of the anticonvulsant and to increase seizure activity. Although the contribution of the vinca alkaloids has not been established, dosage adjustment of phenytoin, based on serial blood level monitoring, may need to be made when it is used in combination with vincristine sulfate.

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 subfamily, or in

patients with hepatic dysfunction (see section 4.2). Inhibitors like ketoconazole and inducers like St. John's wort should be given cautiously. This interaction is presumed to be related to inhibition of the metabolism of vincristine sulfate.

Concomitant administration of azole antifungals (e.g., itraconazole, voriconazole, posaconazole, isavuconazole and fluconazole) with vincristine may increase the plasma concentrations of vincristine, which can lead to an early onset and/or increased severity of neurotoxicity and other side effects (see section 4.4). Therefore, azole antifungals should be used with caution in patients receiving vincristine and should only be used when there are no alternative antifungal treatment options available or when the potential benefits outweigh the risks of the combination. Patients should be closely monitored for adverse effects with concomitant use.
Although not studied *in vitro* or *in vivo*, voriconazole may increase the plasma concentrations of the vinca alkaloids including vincristine sulfate and lead to neurotoxicity. Therefore, it is recommended that dose adjustment of vincristine sulfate be considered.

L-asparaginase
When vincristine sulfate is used in combination with L-asparaginase, it should be given 12 to 24 hours before administration of the enzyme in order to minimise toxicity, since administering L-asparaginase first may reduce hepatic clearance of vincristine sulfate.

Radiation therapy
When chemotherapy is being given in conjunction with radiation therapy through portals which include the liver, the use of vincristine sulfate should be delayed until radiation therapy has been completed.

Methotrexate
Vincristine sulfate appears to increase the cellular uptake of methotrexate by malignant cells and this principle has been applied in high-dose methotrexate therapy.

Dactinomycin
Severe hepatotoxicity, including veno-occlusive disease has been reported in patients treated with a combination of vincristine sulfate and dactinomycin for renal carcinoma.

Live vaccines
Concomitant use of vincristine sulfate with a live virus vaccine may potentiate the replication of the virus and increase the adverse reactions of the vaccine virus and/or reduce the antibody response of the patient to the vaccine itself because normal defense mechanisms can be suppressed by treatment with vincristine sulfate. Immunisation of such patients should be performed with extreme caution, and only after a thorough evaluation of the haematological picture and with the consent of the doctor who is carrying out the vincristine sulfate therapy. The lapse of time between the suspension of the drug that causes immunosuppression and the recovery of the patient's capacity to respond to the vaccine depends on many different factors and is estimated to vary from a period of 3 months to 1 year.

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.

Pregnancy
Caution is necessary with the use of all oncolytic drugs during pregnancy. Both men and women receiving vincristine sulfate should be informed of the potential risk of adverse effects. Reliable methods of contraception or abstinence are recommended.

Vincristine sulfate can cause foetal harm following maternal or paternal exposure, although there are no adequate and well-controlled studies. Studies in animals have shown vincristine sulfate can induce teratogenic effects as well as embryolethality (see section 5.3).

If vincristine sulfate is used during pregnancy or if the patient becomes pregnant while receiving this medicinal product she should be informed of the potential hazard to the foetus.

There are no or limited amount of data from the use of vincristine sulfate in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3.)

Breast-feeding
There is insufficient information on the excretion of vincristine sulfate in human breast milk. Because of the potential for serious adverse reactions due to vincristine sulfate in nursing infants, the mother should be advised not to breast-feed while on vincristine sulfate therapy and for 1 month following last dose of treatment or to discontinue/abstain from vincristine sulfate therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
Based on clinical reports, male and female fertility may be compromised (see section 4.4). It is recommended to discuss fertility preservation with men and women prior to treatment.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

In general, adverse reactions are reversible and are related to dosage size 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 vincristine sulfate are employed, the adverse reactions of granulocytopenia, neuritic pain, and constipation are usually of short duration (i.e., less than 7 days). When the dosage is reduced, these reactions may lessen or disappear. They seem to be increased when the calculated amount of medicinal product is given in divided doses. Other adverse reactions, such as alopecia, 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, but the neuromuscular difficulties may persist for prolonged periods in some patients. Re-growth of hair may occur while maintenance therapy continues.

The reported adverse reactions are listed below by MedDRA system Organ Class and by frequency. Frequencies are defined as: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), and Frequency not known (cannot be estimated from available data).

System Organ Class	**Very Common**	**Common**	**Uncommon**	**Frequency not known**
Infections and infestations				Infection, Sepsis, Neutropenic sepsis
Neoplasms benign, malignant and unspecified				Secondary malignancies
Blood and lymphatic system disorders	Thrombocytopenia[a], Anaemia			Granulocytopenia, Neutropenia, Haemolytic anaemia
Immune system disorders				Anaphylactic reaction[b], Oedema[b]
Endocrine disorders				Inappropriate antidiuretic hormone secretion[c]
Metabolism and nutrition disorders	Decreased appetite			Hyperuricaemia
Nervous system disorders[d]	Peroneal nerve palsy, Paraesthesia		Coma	Paralysis, Seizure[e], Cranial nerve palsies multiple[f], Sensory loss, Areflexia, Neuralgia, Nystagmus, Ataxia, Balance disorder, Gait disturbance, Dizziness, Headache, Paresis, Motor dysfunction
Eye disorders				Blindness transient, Optic atrophy[g]
Ear and labyrinth disorders				Deafness[h], Vertigo
Cardiac disorders				Myocardial infarction[i],

System Organ Class	Very Common	Common	Uncommon	Frequency not known
				Coronary artery disease[i]
Vascular disorders				Hypotension, Hypertension
Respiratory, thoracic and mediastinal disorders		Oropharyngeal pain		Acute respiratory distress syndrome, Bronchospasm, Dyspnoea
Gastrointestinal disorders	Constipation[j], Abdominal pain, Vomiting, Nausea	Paralytic ileus[k], Diarrhoea		Intestinal perforation, Gastrointestinal necrosis, Mouth ulceration, Salivary gland pain
Hepatobiliary disorders				Venoocclusive liver disease[l]
Skin and subcutaneous tissue disorders	Alopecia			Rash[b]
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[m]		Polyuria, Dysuria, Atonic urinary bladder
General disorders and administration site conditions				Pyrexia, Injection site reaction (see section 4.2)
Investigations	Weight decrease			

a. If thrombocytopenia is present when treatment begins, it may actually improve before the appearance of marrow remission.
b. Reported in patients receiving vincristine sulfate as part of a multi-drug chemotherapy regimen.
c. There is a high urinary sodium excretion in the presence of hyponatraemia, renal or adrenal disease, hypotension, dehydration, azotaemia and clinical oedema are absent. With fluid deprivation, improvement occurs in the hyponatraemia and in the renal loss of sodium.
d. Often dose limiting.
e. Frequently with hypertension. Several instances of convulsions followed by coma have been reported in children.
f. Especially affecting the extra-ocular and laryngeal muscles.
g. With blindness.

h. Partial or total, temporary or permanent. Manifestations also include difficulties with balance, including dizziness, nystagmus and vertigo. Particular caution is warranted when vincristine sulfate is used in combination with other agents known to be ototoxic, such as platinum-based drugs.
i. Reported in association with chemotherapy combinations that included vincristine sulfate when given to patients previously treated with mediastinal radiation. Causality has not been established.
j. Constipation may take the form of upper colon impaction and the rectum may be found to be empty on physical examination.
k. Paralytic ileus may occur particularly in young children. The ileus will reverse itself upon temporary discontinuance of vincristine sulfate and with symptomatic care.
l. Especially in children.
m. 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 sulfate.

Neoplasms benign, malignant and unspecified (including cysts and polyps): The occurrence of secondary malignancies has been reported rarely in patients treated with vincristine sulfate in association with other anticancer drugs known to be carcinogenic.

Blood and lymphatic system disorders: Granulocytopenia and neutropenia; vincristine does not appear to have any constant or significant effect upon the platelets or the red blood cells, however, anaemia, haemolytic anaemia and thrombocytopenia have been reported. Clinical consequences of granulocytopenia may be fever, infections and sepsis. There have been occasional reports of fatal infections during vincristine therapy.

Nervous system disorders: Frequently, there appears to be a sequence in the development of neuromuscular side effects. Initially, one may encounter only sensory impairment and paraesthesia. With continued treatment, neuritic pain may appear and later, motor difficulties. No reports have yet been made of any agent that can reverse the neuromuscular manifestations of vincristine sulfate.

Ear and labyrinth disorders: Treatment with vinca alkaloids has resulted rarely in both vestibular and auditory damage to the eighth cranial nerve.

Gastro-intestinal disorders: The constipation which may be encountered responds well to such usual measures as enemas and laxatives. Colicky abdominal pain, coupled with an empty rectum, may mislead the clinician. A flat film of the abdomen is useful in demonstrating this condition. A routine prophylactic regimen against constipation is recommended for all patients receiving vincristine sulfate.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Side effects following the use of vincristine are dose related. In children under 13 years of age, death has occurred following doses of vincristine that were 10 times those recommended for

therapy. Severe symptoms may occur in this patient group following dosages of 3 to 4 mg/m². Adults can be expected to experience severe symptoms after single doses of 3 mg/m² or more. Therefore, following administration of doses higher than those recommended patients can be expected to experience side-effects in an exaggerated fashion.

Supportive care should include the following: (a) prevention of side-effects resulting from the syndrome of inappropriate antidiuretic hormone secretion (this would include restriction of fluid intake and perhaps the administration of a diuretic affecting the function of the loop of Henle and the distal tubule); (b) administration of anticonvulsants; (c) use of enemas or cathartics to prevent ileus (in some instances, decompression of the gastrointestinal tract may be necessary); (d) monitoring the cardiovascular system; (e) determining daily blood counts for guidance in transfusion requirements.

Folinic acid has been observed to have a protective effect in normal mice which were administered lethal doses of vincristine sulfate. Isolated case reports suggest that folinic acid may be helpful in treating humans who have received an overdose. A suggested schedule is to administer 100 mg 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 sulfate 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 the above-mentioned supportive measures.

Most of an intravenous dose of vincristine sulfate is excreted into 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.

Enhanced faecal excretion of parenterally administered vincristine sulfate has been demonstrated in dogs pre-treated with cholestyramine. There are no published clinical data on the use of cholestyramine as an antidote in humans.

There are no published clinical data on the consequences of oral ingestion of vincristine sulfate. Should oral ingestion occur, the stomach should be evacuated followed by oral administration of activated charcoal and a cathartic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent - vinca alkaloid. ATC Code: L01C A02

Mechanism of action

Vincristine sulfate is an antineoplastic drug with broad-spectrum anti-tumour activity in man. The drug may act by mitotic inhibition, causing an arrest of cell division in metaphase. The drug is relatively marrow-sparing and is thus suitable for use in combination with other cancer chemotherapeutic agents.

5.2 Pharmacokinetic properties

Vincristine sulfate is poorly absorbed orally. The clearance of the drug after rapid intravenous injection follows a triphasic decay pattern: a very rapid steep descent (alpha phase); a narrow-middle

region (beta-phase) and a much longer terminal region (gamma phase). The terminal phase half-life of the drug varies from 15-155 hours.

Dosing with the drug more frequently than once weekly is therefore probably unnecessary.

Vincristine sulfate is primarily excreted by the biliary route.

Patients with impaired hepatic or biliary function, as evidenced by a raised serum alkaline phosphatase, have been shown to have a significantly prolonged vincristine sulfate elimination half-life.

5.3 Preclinical safety data

Both *in vivo* and *in vitro* laboratory tests have failed to demonstrate conclusively that this product is mutagenic. No evidence of carcinogenicity was found following intraperitoneal administration in rats and mice, although this study was limited.

In several animal species, vincristine sulfate can include teratogenic effects, as well as embryo lethality, with doses that are non-toxic to the pregnant animal. Mice treated with a single IP administration of 0.25 to 0.35 mg/kg, vincristine sulfate on day 9 of pregnancy, showed foetal resorption rates of 49% to 57% (control: 6%) and 32% to 66% of surviving foetuses showed malformations.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Mannitol, Water for injections

6.2 Incompatibilities

It is not recommended that vincristine sulfate should be mixed with any other drug and should not be diluted in solutions that raise or lower the pH outside the range 3.5 to 5.5. It should not be mixed with anything other than normal saline or 5% glucose solution.

Furosemide both in syringe and injected sequentially into Y-site with no flush between, results in immediate precipitation.

6.3 Shelf life

2 years.

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 solution or 5% glucose solution in infusion bags and protected from light. If stored under normal light at 25 °C, when diluted with 0.9% sodium chloride solution or 5% glucose solution, 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 in a refrigerator (2ºC – 8 ºC).
Keep the vial in the outer carton, in order to protect from light.
For storage conditions after first opening and dilution, see section 6.3.

6.5 Nature and contents of container

2 ml Type I clear glass vials, with rubber closures and aluminium caps in packs of 5 vials.

2 ml Type I clear Onco-Tain® vials, with rubber closures and aluminium caps in packs of 5 vials.

2.25 ml Type I clear glass, graduated, barrel syringes with luer lock as a single syringe pack.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Cytotoxic Handling Guidelines

Administration:

Should be administered only by or under the direct supervision of a qualified physician who is experienced in the use of cancer chemotherapeutic agents.

Vincristine sulfate can be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection, see section 6.3.

Preparation (Guidelines)

1. Chemotherapeutic agents should be prepared for administration only by professionals who have been trained in the safe use of preparation.

2. Operations such as reconstitution of powder and transfer to syringes should be carried out only in the designated area. The work surface should be covered with disposable plastic-backed absorbent paper.

3. The personnel carrying out these procedures should be adequately protected with clothing, masks, gloves and eye shield.

4. Pregnant personnel are advised not to handle chemotherapeutic agents.

5. Use Luer-lock fittings on all syringes and sets. Large bore needles are recommended to minimise the pressure and the possible formation of aerosols. The latter may be reduced by the use of a venting needle.

6. 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.

7. Adequate care and precaution should be taken in the disposal of items (syringes, needles, etc.) used to reconstitute cytotoxic drugs.

8. Whenever solution and container permit, parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Contamination

(a) Precautions should be taken to avoid the drug accidentally coming into contact with the eyes. If accidental contamination occurs, severe irritation (or if the drug was delivered under pressure, even corneal ulceration) may result. In the event of contact with the skin or eyes, the affected area should be washed with copious amounts of water or normal saline thoroughly and immediately. A bland cream may be used to treat the transient stinging of skin. Medical advice should be sought if the eyes are affected.

(b) In the event of spillage, operators should put on gloves and mop the spilled material with a sponge kept in the area for that purpose. Rinse the area twice with water. Put all solutions and sponges into a plastic bag and then seal it.

Disposal

Syringes, containers, absorbent materials, solution and any other contaminated material should be placed in a thick plastic bag or other impervious container and incinerated.

7. MARKETING AUTHORISATION HOLDER

Hospira UK Limited
Walton Oaks
Walton-On-The-Hill
Dorking Road
Tadworth
Surrey
KT20 7NS
UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 04515/0008.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/11/2007

10 DATE OF REVISION OF THE TEXT

16/09/2024