Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vincristine Sulfate 1mg/ml Solution for Injection or Infusion

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/ infusion.

A sterile colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vincristine Sulfate is used primarily as a component of various chemotherapeutic regimens for the treatment of acute leukaemias. It has also been used in conjunction with other oncolytic drugs in the treatment of Hodgkin's Disease, all forms of lymphoma, Wilm's tumour, sarcomas and tumours of the breast, brain and lung.

4.2 Posology and method of administration

Posology

The following dosage regimens have been used:

Acute Leukaemia

Adults: The suggested dose is 1.4 - 1.5 mg/m^2 given on a weekly basis to a maximum weekly total dose of 2 mg.

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

Children: The suggested dose is 1.4 – 2.0 mg/m^2 given on a weekly basis beginning with the lowest dose in the range 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 once a week.

Once the remission has occurred, dosage may often be reduced for maintenance therapy.

Other Tumours
25 micrograms/kg body weight weekly until a response is observed and 5-10 micrograms/kg body weight thereafter for maintenance.

Use in the elderly
As for use in adults.

Use in hepatic impairment
A 50% 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 use only. Can be fatal if administered intrathecally (see sections 4.3 and 4.4). It should only be administered by individuals experienced in vincristine administration.

FOR INTRAVENOUS USE ONLY.
FATAL IF GIVEN BY OTHER ROUTES (see section 4.4)

In case of accidental administration by the intrathecal route, see section 4.4.

Vincristine Sulfate is administered by intravenous push or infusion at weekly intervals, the precise dose being determined by body weight.

Great care should be exercised in calculating 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 infusion (IV) or intravenous injection (IV push) 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. In general, individual doses should not exceed 2mg; and white cell counts should be carried out before and after giving each dose.

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 of normal saline (50 ml sodium chloride 9 mg/ml (0.9%)) or 5% Dextrose (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 5% Dextrose). 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 and 4.4).

Alternatively, Vincristine Sulfate may be injected directly into a vein over about one minute.

Syringes containing this product should be overlabelled with the warning label provided: **'FOR INTRAVENOUS USE ONLY. FATAL IF GIVEN BY OTHER ROUTES**.

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

FOR INTRAVENOUS USE ONLY.
FATAL IF GIVEN BY OTHER ROUTES (see section 4.4)

- Hypersensitivity to vincristine sulfate or to any of the excipients listed in section 6.1.
- Use in the management of non-malignant disease, except for immunosuppression.
- Use in the presence of untreated infection.
- Patients with the demyelinating form of Charcot-Marie-Tooth syndrome must not be given vincristine sulfate.

4.4 Special warnings and precautions for use

Vincristine Sulfate should only be administered under the direction of a specialist oncology service having the facilities for regular monitoring of clinical biochemical and haematological effects during and after administration.

Vincristine Sulfate is for intravenous use only. Can be fatal if administered intrathecally (see sections 4.2 and 4.3).

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 administration:**

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.

Syringes containing this product should be overlabelled with the warning label provided: '**FOR INTRAVENOUS USE ONLY. FATAL IF GIVEN BY OTHER ROUTES**

Vincristine Sulfate is a vesicant and may cause a severe local reaction or extravasation. If leakage into the surrounding tissue should occur during I.V. administration of Vincristine Sulfate, it 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
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, 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. Vincristine sulfate should only be used with caution in patients with bone marrow depression or in those having infiltration of marrow by malignant cells.

Urate nephropathy
Acute uric acid nephropathy, which may occur after administration of oncolytic agents, has also been reported with Vincristine Sulfate.

Neurological
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).

Gastrointestinal

A routine prophylactic regimen against constipation is recommended for all patients receiving vincristine sulfate. Paralytic ileus may occur, particularly in young children. The ileus will reverse itself upon temporary discontinuance of vincristine sulfate and with symptomatic care.

Hepatic impairment
An increase in the severity of side-effects may be experienced by patients with liver disease sufficient to decrease biliary excretion. The elimination of Vincristine Sulfate may be reduced in the presence of impaired hepatic or biliary function and the dose must be decreased accordingly (see section 4.2).

Carcinogenicity
There is a possibility that this product may exert a carcinogenic effect with long term therapy, although to date no positive evidence is available.

Mutagenicity
Both *in vivo* and *in vitro* laboratory tests have failed to demonstrate conclusively that the 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 these studies were limited.

Eye 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

Allopurinol, Pyridoxine and Isoniazid
Allopurinol, pyridoxine and isoniazid may increase the incidence of cytotoxic induced bone marrow depression. The mechanism for this potentiation has not been fully classified.

Peripheral Nervous System drugs
The neurotoxicity of Vincristine Sulfate may be additive with that of other drugs acting on the peripheral nervous system.

Vinca Alkaloids and other Ototoxic drugs
Treatment with vinca alkaloids has resulted rarely in both vestibular and auditory damage to the eighth cranial nerve. Particular caution is warranted when vincristine sulfate is used in combination with other agents known to be ototoxic, such as the platinum-containing oncolytics.

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.

Mitomycin-C
Acute shortness of breath and severe bronchospasm have been reported following 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 two 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). Concurrent administration of vincristine sulfate with itraconazole or fluconazole (known inhibitors of the metabolic pathway) carries the risk of increased vincristine toxicity because of the decreased hepatic metabolism induced by fluconazole. Concurrent administration of vincristine sulfate with itraconazole or fluconazole have been reported to cause an earlier onset and/or an increased severity of neuromuscular side-effects (see section 4.8). Herbal preparations containing St John's Wort (Hypericum perforatum) should be used with caution whilst taking vincristine sulfate due to a potential risk of decreased plasma concentrations, the enzyme-inducing effects of St John's wort (Hypericum perforatum) may increase the metabolism and decrease the effects of vincristine sulfate.

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 - 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.

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

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 should be informed of the potential risk of adverse effects.

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).

Vincristine Sulfate is not recommended during pregnancy. Vincristine sulfate can cause foetal harm when administered to pregnant women, 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 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.

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 breast-feeding 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 and cumulative dosage. The use of small amounts of vincristine sulfate daily for long periods is not advised. The most common adverse reaction is alopecia; the most troublesome adverse reactions are neuromuscular in origin.

When single weekly doses of the drug are employed, the adverse 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 drug 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. Generalized sensorimotor dysfunction may become progressively more severe with continued treatment. In most instances, they disappear by about the sixth week after discontinuation of treatment, but the neuromuscular difficulties may persist for prolonged periods in some patients. Regrowth of hair may occur while maintenance therapy continues.

The reported adverse reactions are listed below by 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 (incl cysts and polyps)				Secondary malignancies
Blood and lymphatic system disorders	Thrombocytopenia[a], Anaemia,			Granulocytopenia, Neutropenia, Haemolytic anaemia
Immune system disorders				Anaphylactic reaction[b], Angioedema[b], Oedema[b]
Endocrine disorders				Inappropriate antidiuretic hormone secretion[c]
Metabolism and nutrition disorders	Hyponatraemia, Decreased appetite			Dehydration, Hyperuricaemia
Nervous system disorders[d]	Peroneal nerve palsy, Paraesthesia		Coma	Paralysis, Seizure[e], Cranial nerve palsies multiple[f], Sensory loss, Areflexia, Neuralgia, Nerve injury, Nystagmus, Ataxia, Balance disorder, Gait disturbance, Dizziness,

				Headache, Paresis, Motor dysfunction, Leukoencephalopathy, Encephalopathy
Eye disorders				Blindness transient, Optic atrophy[g]
Ear and labyrinth disorders				Deafness[h], Vertigo
Cardiac disorders				Myocardial infarction[i], 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	Ileus paralytic[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[m]	Myalgia, Bone pain	Pain in jaw		Muscle atrophy, Pain in extremity, Back pain
Renal and urinary disorders		Urinary retention[n]		Urate nephropathy, Polyuria, Dysuria, Atonic urinary bladder
General disorders and administration site conditions				Pyrexia, Injection site reaction
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. Manifested by high urinary sodium excretion in the presence of hyponatraemia, renal or adrenal disease, hypotension, and dehydration. 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 Pain in these areas may be severe.
n Other drugs known to cause urinary retention (particularly in the elderly) should, if possible, be discontinued for the first few days following administration of vincristine sulfate.

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

The occurrence of secondary malignancies has been reported rarely in patients treated with vincristine 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 paraesthesiae. With continued treatment, neuritic pain may appear and later, motor difficulties. No reports have yet been made of any agent that 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.

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 HPRA Pharmacovigilance;
Website: www.hpra.ie.

4.9 Overdose

Side effects of Vincristine Sulfate are dose related and are exaggerated by overdosage. There is, as yet, no antidote for Vincristine Sulfate. 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/m^2. Adults can be expected to experience severe symptoms after single doses of 3 mg/m^2 or more. Therefore, following administration of doses higher than those recommended patients can be expected to experience side-effects in an exaggerated fashion.

Support therapy should be directed to the prevention of the side effects resulting from hypersecretion of antidiuretic hormone by restriction of fluid intake and possibly the use of an appropriate diuretic. Anticonvulsants, e.g. phenobarbitone may be necessary for control of seizure and cathartics administered to prevent ileus. Use of enemas or cathartics to prevent ileus (in some instances, decompression of the gastrointestinal tract may be necessary.

Routine cardiovascular monitoring is recommended together with daily haematology 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 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. Tissue levels of vincristine sulfate 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 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.

There are no published clinical data on the consequences of oral ingestion of vincristine. 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: L01CA02.

Mechanism of action

Although the mechanism of action has not been definitely established, Vincristine appears to bind to or crystallize critical microtubular proteins of the mitotic spindle, thus preventing their proper polymerization and causing metaphase arrest. In high concentrations, the drug also exerts complex effects on nucleic acid and protein synthesis. Vincristine exerts some immuno-suppressive activity.

5.2 Pharmacokinetic properties

Absorption

Vincristine sulfate is not reliably absorbed from the gastro-intestinal tract. After intravenous administration it disappears rapidly from the blood. It is extensively protein bound and it is reported to be concentrated in blood platelets. It is metabolised in the liver and excreted primarily in the bile - about 70% of a dose is found in faeces, as unchanged drug and metabolites, over 72 hours. Some also appears in the urine. Vincristine does not appear to cross the blood-brain barrier in significant amounts.

Elimination

Following rapid I.V. administration of vincristine sulfate, serum concentrations of the drug appear to decline in a triphasic manner. The terminal elimination half-life of vincristine sulfate has ranged from 10.5-155 hours.

5.3 Preclinical safety data

Both *in vivo* and *in vitro* tests have failed to demonstrate conclusively that vincristine sulfate 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 induce 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 cannot be excluded.

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. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

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

6.3 Shelf life

Unopened: 2 years
Once opened: use immediately

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 in a refrigerator (2°C-8°C).

Keep 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 stoppers containing 2 ml of solution in packs of 5 vials.Each vial is wrapped in a clear, plastic (ONCO-TAIN®) protective sleeve.

6.6 Special precautions for disposal and other handling

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.
For single use only, discard any unused contents.

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 of normal saline (50 ml sodium chloride 9 mg/ml (0.9%)) or 5% Dextrose.

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.

Further Information
Cytotoxic Handling Guidelines

<u>Administration:</u>
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 0.9% Sodium Chloride or 5% Dextrose, 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) In the event of contact with the skin or eyes, the affected area should be washed with copious amounts of water or normal saline. 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 up 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

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0822/232/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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