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Summary of Product Characteristics last updated on the eMC: 07/05/2009

Vincristine Sulphate 1mg/ml Injection (5mg/5ml) (Hospira UK Ltd)

1. NAME OF THE MEDICINAL PRODUCT

Vincristine Sulphate 1 mg/ml Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains 1.0 mg of vincristine sulphate

Each 5ml presentation contains 5 mg of vincristine sulphate

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Solution for injection

A sterile, colourless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vincristine sulphate 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 but the medicinal product is not recommended as primary treatment of this disorder. Recommended weekly doses of vincristine 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

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

FOR INTRAVENOUS USE ONLY

FATAL IF GIVEN BY ANY OTHER ROUTE

See Section 4.4 Special warnings and precautions for use.

Vincristine sulphate is administered by intravenous injection 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 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.

Vincristine Sulphate Injection may be injected into the tubing or side arm of a free-flowing intravenous infusion or directly into a vein over a one-minute period. For safety reasons when administering Vincristine Sulphate Injection into a side arm of a fast running infusion, please ensure that pressure is maintained on the syringe plunger during administration, to avoid back pressure from the infusion forcing the plunger out of the syringe barrel. Care should be taken to avoid extravasation as this may cause local ulceration.

The following dosage regimens have been used:

Adults: The drug is usually 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, 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 sulphate is recommended for patients having a direct serum bilirubin value above 3 mg/100 ml (51 micromol/l).

Caution: If leakage into surrounding tissue should occur during intravenous administration of vincristine, 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 the 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.

4.3 Contraindications

Intrathecal administration of vincristine sulphate is usually fatal.

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

As Vincristine Sulphate Injection contains benzyl alcohol it must not be given to premature babies or neonates.

Vincristine Sulphate Injection should not be given to patients who have shown signs of hypersensitivity to vincristine or to any of the excipients

Careful notice should also be given to those conditions listed in Section 4.4 Special warnings and precautions for use.

4.4 Special warnings and precautions for use

Warnings

This preparation is for intravenous use only. It should be administered by physicians experienced

in the administration of vincristine sulphate. Vincristine sulphate should not be given by intrathecal, intramuscular or subcutaneous injection. The intrathecal administration of vincristine sulphate usually results in death.

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

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 is mistakenly given by the intrathecal route, the following treatment should be initiated **immediately after the injection:**

1. Removal of as much 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 sulphate is a vesicant and may cause severe local reaction or extravasation, see *Caution* in Section 4.2, Posology and Method of Administration.

As Vincristine Sulphate Injection contains benzyl alcohol it may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

Precautions

Leucopenia is less likely following therapy with vincristine sulphate 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 leucopenia, 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 sulphate warrants careful consideration.

Acute uric acid nephropathy, which may occur after administration of oncolytic agents, has also been reported with vincristine sulphate.

As vincristine sulphate 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 sulphate 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 sulphate.

Both in vivo and in vitro laboratory tests have failed to demonstrate conclusively that this product is mutagenic. Fertility following treatment with vincristine alone for malignant disease has not been studied in humans. Clinical reports of both male and female patients who received multiple-

agent chemotherapy that included vincristine indicate that azoospermia and amenorrhoea can occur in postpubertal 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.

Patients who received vincristine chemotherapy in combination with anticancer drugs known to be carcinogenic have developed second malignancies. The contributing role of vincristine 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.

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

Vincristine can cause foetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant while receiving vincristine (see Section 4.6 Pregnancy and lactation and Section 5.3 Preclinical safety data).

4.5 Interaction with other medicinal products and other forms of interaction

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

The neurotoxicity of vincristine sulphate may be additive with that of other drugs acting on the peripheral nervous system.

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 injected and may occur up to 2 weeks following the dose of mitomycin. Progressive dyspnoea, requiring chronic therapy, may occur. Vincristine should not be re-administered.

The simultaneous oral or intravenous administration of phenytoin and antineoplastic chemotherapy combinations, that included vincristine sulphate, 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.

Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP 3A subfamily, or in patients with hepatic dysfunction. Concurrent administration of vincristine sulphate with itraconazole (a known inhibitor of the metabolic pathway) has been reported to cause an earlier onset and/or an increased severity of neuromuscular side-effects (see Section 4.8 Undesirable effects). This interaction is presumed to be related to inhibition of the metabolism of vincristine.

When vincristine sulphate 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.

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

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

4.6 Pregnancy and lactation

Usage in pregnancy: Caution is necessary with the use of all oncolytic drugs during pregnancy.

Vincristine can cause foetal harm when administered to a pregnant woman, although there are no adequate and well-controlled studies (see Section 5.3 Preclinical safety data). Women of childbearing potential should be advised to avoid becoming pregnant while receiving vincristine.

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.

Usage in nursing mothers: It is not known whether vincristine is excreted in human breast milk. Because of the potential for serious adverse reactions due to vincristine in nursing infants, a decision should be made whether to discontinue nursing or vincristine, taking into account the importance of the medicinal product to the mother.

4.7 Effects on ability to drive and use machines

Not applicable.

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 are employed, the adverse reactions of leucopenia, 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 following adverse reactions have been reported:

Blood and lymphatic system disorders: Leucopenia; vincristine does not appear to have any constant or significant effect upon the platelets or the red blood cells, however, anemia and thrombocytopenia have been reported. If thrombocytopenia is present when treatment with vincristine sulphate is begun, it may actually improve before the appearance of marrow remission.

Endocrine disorders: Rare occurrences of a syndrome attributable to inappropriate anti-diuretic hormone secretion have been observed in patients treated with vincristine. 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.

Nervous system disorders (often dose limiting): Neuritic pain, sensory loss, paraesthesiae, difficulty in walking, slapping gait, loss of deep tendon reflexes, ataxia, paresis, foot drop and cranial nerve palsies, especially ocular palsies and laryngeal nerve paralysis. 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 can reverse the neuromuscular manifestations of vincristine sulphate. Convulsions, frequently with hypertension, have been reported in a few patients receiving vincristine. Several instances of convulsions followed by coma have been reported in children.

Eye disorders: Transient cortical blindness and optic atrophy with blindness have been reported.

Ear and labyrinth disorders: Treatment with vinca alkaloids has resulted rarely in both vestibular and auditory damage to the eighth cranial nerve. Manifestations include partial or total deafness, which may be temporary or permanent, and difficulties with balance, including dizziness, nystagmus and vertigo. Particular caution is warranted when vincristine sulphate is used in combination with other agents known to be ototoxic, such as the platinum-containing oncolytics.

Cardiac disorders: Chemotherapy combinations which have included vincristine, when given to patients previously treated with mediastinal radiation, have been associated with coronary artery disease and myocardial infarction. Causality has not been established.

Vascular disorders: Hypertension and hypotension have occurred.

Respiratory disorders: Acute shortness of breath and severe bronchospasm have been reported following the administration of vinca alkaloids (see Section 4.5 Interaction with other medicinal

products and other forms of interaction).

Gastro-intestinal disorders: Constipation, abdominal cramps, paralytic ileus, diarrhoea, weight loss, nausea, vomiting, oral ulceration, intestinal necrosis and/or perforation, and anorexia have occurred. The constipation which may be encountered responds well to such usual measures as enemas and laxatives. Constipation may take the form of upper colon impaction and the rectum may be found to be empty on physical examination. 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 sulphate. Paralytic ileus may occur, particularly in young children. The ileus will reverse itself upon temporary discontinuance of vincristine and with symptomatic care.

Skin and subcutaneous tissue disorders: Alopecia, rash.

Musculoskeletal, connective tissue and bone disorders: Muscle wasting, 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.

Renal and urinary disorders: Polyuria, dysuria and urinary retention due to bladder atony have occurred. 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.

General disorders: Rare cases of allergic-type reactions, such as anaphylaxis, rash and oedema, temporally related to vincristine therapy have been reported in patients receiving vincristine as a part of multi-drug chemotherapy regimens.

Other: Fever, headache, injection site reaction (see Section 4.2 Posology and method of administration).

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 antidiruetic hormone secretion (this would include restriction of fluid intake and perhaps the administration of a diuretic affecting the function of Henle's loop 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. 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 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 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 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. 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

Vincristine is an antineoplastic drug with broad-spectrum anti-tumor 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 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 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 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 can include teratogenic effects, as well as embryolethality, with doses that are non-toxic to the pregnant animal.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, benzyl alcohol (9 mg per ml), Water for Injections

6.2 Incompatibilities

It is not recommended that vincristine sulphate 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. Furosemide both in syringe and injected sequentially into Y-site with no flush between, results in immediate precipitation.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Store at 2 - 8°C. Keep container in the outer carton.

6.5 Nature and contents of container

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

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

6.6 Special precautions for disposal and other handling

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.

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.

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

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

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 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

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Royal Leamington Spa

Warwickshire

CV31 3RW

8. MARKETING AUTHORISATION NUMBER(S)

PL 04515/0043

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

October 1995/ 2nd December 2008

10. DATE OF REVISION OF THE TEXT

2nd December 2008