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VINBLASTINE SULFATE 1MG/ML SOLUTION

1.name of the medicinal product

Vinblastine Sulfate 1 mg/ml solution for injection

2. Qualitative and quantitative composition

Each 1 ml contains 1.0 mg of vinblastine sulfate.

Each 10 ml presentation contains 10 mg of vinblastine sulfate.

Excipient with known effect

Each 10 ml vial contains approximately 35 mg (1.5 mmol) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

A clear, colourless sterile solution.

4. Clinical particulars

4.1 Therapeutic indications

Vinblastine sulfate is a cytotoxic drug that arrests cell growth at the metaphase. Its actions are more pronounced on the rapidly dividing cell than on the normal cell. It appears to act, like vincristine, by binding to the microtubular proteins of the mitotic spindle, preventing polymerisation.

Information available at present suggests that vinblastine sulfate may be useful, either alone or in combination with other oncolytic drugs, for the treatment of: Hodgkin's disease; non-Hodgkin's lymphoma; carcinoma of the breast; methotrexate-resistant choriocarcinoma; renal cell carcinoma; testicular teratoma and seminoma; histiocytosis X. Other neoplasms occasionally show a marked response to vinblastine sulfate, but less frequently than the more susceptible conditions listed above.

4.2 Posology and method of administration

Posology

The recommended dose for adults, the elderly and children is 6 mg/m^2, usually administered no more frequently than once every seven days. For testicular tumours, the dosage may be increased to 0.2 mg/kg administered on each of two consecutive days every three weeks.

To minimise the possibility of extravascular spillage, it is suggested that the syringe and needle be rinsed with venous blood before withdrawal. The dose should not be diluted in large volumes of diluent (ie, 100 to 250 ml) or given intravenously for prolonged periods (ranging from 30 to 60 minutes or more), since this frequently results in irritation of the vein and increases the chance of extravasation.

Because of the enhanced possibility of thrombosis, it is considered inadvisable to inject a solution of vinblastine sulfate into an extremity in which the circulation is impaired, or potentially impaired, by such conditions as compressing or invading neoplasm, phlebitis or varicosity.

Patients with hepatic impairment

As vinblastine is excreted principally by the liver, toxicity may be increased when there is hepatic insufficiency and it may be necessary to reduce initial doses in the presence of significantly impaired hepatic or biliary function. A reduction of 50% in the dose is recommended for patients having a direct serum bilirubin value above 3 mg/100 ml.

Patients with renal impairment

Since metabolism and excretion are primarily hepatic, no modification is recommended for patients with impaired renal function.

Vinblastine should not be given intramuscularly, subcutaneously or intrathecally.

Method of administration

The solution may be injected either directly into the vein or into the injection site of a running intravenous infusion. Injection of vinblastine sulfate may be completed in about one minute.

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

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

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

For intravenous use only. Fatal if given by other routes (see section 4.4).

Vinblastine sulfate is contraindicated in patients who are leucopenic. It should not be used in the presence of bacterial infection. Such infections should be brought under control with antiseptics or antibiotics before the initiation of therapy with vinblastine sulfate.

4.4 Special Warnings and precautions for use

Warnings: Vinblastine sulfate must be used only by physicians experienced in cytotoxic chemotherapy.

The following treatment successfully arrested progressive paralysis in a single patient mistakenly given the related vincristine sulfate, intrathecally. This treatment should be initiated immediately:

1. Removal of as much CSF as is safely possible.

2. Flushing with Lactated Ringer's solution by continuous infusion at 150 ml/h, through a catheter in a cerebral lateral ventricle and removed through lumbar access, until fresh plasma became available.

3. Fresh frozen plasma, 25 ml, diluted with 1litre of Lactated Ringer's was then infused similarly at 75 ml/h. The rate of infusion should be adjusted to maintain a spinal fluid protein level of 150 mg/dl.

4. Glutamic acid, 10 g, was given iv over 24 hours, followed by 500 mg tds by mouth for 1 month. Glutamic acid may not be essential.

Vinblastine SHOULD NOT BE GIVEN intramuscularly, subcutaneously or intrathecally.

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

Caution is necessary with the use of vinblastine sulfate during pregnancy. There is insufficient information to assess vinblastine sulfates effect on fertility in men and women. However, aspermia has been reported in man.

Animal studies suggest that teratogenic effects may occur. The drug should not be used in pregnant women unless the expected benefit outweighs the potential risk.

As with other antineoplastic agents, vinblastine may cause a severe local reaction on extravasation. If leakage into the surrounding tissue should occur during intravenous administration of vinblastine sulfate, the injection should be discontinued immediately and any remaining portion of the dose should be introduced into another vein. Local injection of hyaluronidase with the application of heat has been used to disperse the drug in order to minimise discomfort and the possibility of tissue damage.

Liver disease may alter the elimination of vinblastine in the bile, markedly increasing toxicity to peripheral nerves and necessitating a dosage modification in affected patients.

The vial stopper contains dry natural rubber (a derivative of latex), which may cause allergic reactions.

Precautions: Patients should be carefully monitored for infection until the white cell count has returned to normal levels, if leucopoenia with less than 2000 white blood cells per mm^3 occurs following a dose of vinblastine sulfate.

When cachexia or ulcerated areas of the skin are present, a more profound leucopenic response may be produced by vinblastine. Therefore, its use should be avoided in older persons suffering from either of these conditions.

Leucocyte and platelet counts have sometimes fallen precipitously after moderate doses of vinblastine sulfate in patients with malignant cell infiltration of the bone marrow.

Further use of the drug in such patients is inadvisable. Avoid contamination of the eye with vinblastine sulfate solution for injection. If accidental contamination occurs, severe irritation or corneal ulceration may result. The affected eye should be thoroughly irrigated with water immediately.

4.5 Interaction with other medicinal products and other forms of interaction

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

Vinblastine used as part of a combination regimen with mitomycin may result in acute respiratory distress and pulmonary infiltration. Cases of respiratory distress with interstitial pulmonary infiltrates have been reported in patients given a regimen comprising vinblastine, mitomycin, and progesterone (MVP). Acute shortness of breath and severe bronchospasm have been reported following the administration of the 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 a dose of mitomycin. Progressive dyspnoea, requiring chronic therapy, may occur. Vinblastine should not be re-administered.

Co-administration of cisplatin has been reported to cause higher plasma concentrations of vinblastine.

There have been reports of Raynaud's phenomenon and gangrene following co-administration of vinblastine and bleomycin, and of other vascular events (such as myocardial infarction and cerebrovascular accident) following combined treatment with vinblastine, bleomycin and cisplatin.

Erythromycin may increase the toxicity of vinblastine.

Serum levels of anticonvulsants may be reduced by cytotoxic drug regimes, which include vinblastine.

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 vinblastine sulfate with an inhibitor of this metabolic pathway may cause an earlier onset and/or an increased severity of side-effects.

4.6 Fertility, pregnancy and lactation

Pregnancy

Although information on the use of vinblastine during pregnancy is limited, the drug may cause foetal toxicity when administered to pregnant women. The drug causes resorption of foetuses in animals and produces gross foetal abnormalities in surviving offspring. There are no adequate and controlled studies to date using vinblastine in pregnant women, and the drug should be used during pregnancy only in life-threatening situations or severe disease for which safer drugs cannot be used or are ineffective. Women of childbearing potential should be advised to avoid becoming pregnant while receiving the drug. When vinblastine is administered during pregnancy or the patient becomes pregnant while receiving the drug, the patient should be informed of the potential hazard to the foetus.

Fertility

The effect of vinblastine on fertility in humans is not fully known. Aspermia has occurred in some individuals during vinblastine therapy.

Breast-feeding

It is not known whether vinblastine is excreted in human milk. Because of the potential for serious adverse reactions due to vinblastine in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable Effects

The use of small amounts of vinblastine daily for long periods is not advisable, even though the resulting total dosage may be similar to the recommended dosage. Little or no therapeutic advantage has been demonstrated when such regimens have been used and side-effects are increased.

The incidence of side effects with vinblastine sulfate appears to be dose related and most do not persist longer than 24 hours. Neurological effects are uncommon but can occur and may last longer than 24 hours.

Leucopoenia is the most common side effect and dose limiting factor.

The following side effects have been reported:

Blood and lymphatic system disorders: Leucopoenia, thrombocytopenia, anaemia.

Nervous system disorders: Numbness, paraesthesia's, peripheral neuritis, mental depression, loss of deep tendon reflexes, headache, convulsions, 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 vinblastine sulfate is used in combination with other agents known to be ototoxic, such as the platinum-containing oncolytics.

Cardiac disorders: Myocardial infarction, cerebrovascular accident (cases of unexpected myocardial infarction and cerebrovascular accidents have occurred in patients undergoing combination chemotherapy with vinblastine, bleomycin and cisplatin).

Vascular disorders: Hypertension.

Respiratory, thoracic and mediastinal disorders: Acute respiratory distress (including shortness of breath) has been reported when vinblastine is given in combinations with mitomycin (see section 4.5).

Gastrointestinal disorders: Nausea, vomiting, constipation, oral mucosal blistering, diarrhoea, anorexia, abdominal pain, rectal bleeding, pharyngitis, haemorrhagic enterocolitis, bleeding from an old peptic ulcer, ileus, stomatitis. Antiemetics may be used to control nausea and vomiting.

Skin and subcutaneous tissue disorders: Blister (skin), alopecia (usually not total and in some cases the hair regrows during maintenance therapy).

Musculoskeletal and connective tissue disorders: Myalgia, bone pain, jaw pain, tumour pain (pain in tumour-containing tissue).

General disorders and administration site conditions: Malaise, asthenia, dizziness.

Injection site reaction (see section 4.2): Extravasation during intravenous injection may result in cellulitis and phlebitis. In extreme instances sloughing may occur. Syndrome of inappropriate ADH secretion has been reported with higher than recommended doses. Raynaud's phenomenon has occurred when patients are being treated with vinblastine in combination with bleomycin and cisplatin for testicular cancer.

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.

4.9 Overdose

Side effects following the use of vinblastine are dose related. Therefore, following administration of more than the recommended dose, patients can be expected to experience these effects in an exaggerated fashion.

In addition, neurotoxicity similar to that seen with vincristine sulfate may be observed.

Treatment: Supportive care should include: (1) prevention of the side effects that result from the syndrome of inappropriate secretion of antidiuretic hormone. This includes restriction of fluid intake and perhaps the use of a diuretic acting on the loop of Henle and distal tubule function; (2) administration of an anticonvulsant; (3) prevention and treatment of ileus; (4) monitoring the patient's cardiovascular

system; and (5) daily blood counts for guidance in transfusion requirement.

The major effect of excessive doses of vinblastine will be on granulocytopoeisis, and this may be life-threatening.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vinca alkaloids and analogues,

Mechanism of action

Although the mechanism of action has not been definitely established, vinblastine appears to bind to or crystallise critical microtubular proteins of the mitotic spindle, thus preventing their proper polymerisation and causing metaphase arrest. In high concentrations, vinblastine also exerts complex effects on nucleic acid and protein synthesis. Vinblastine reportedly also interferes with amino acid metabolism by blocking cellular utilisation of glutamic acid and thus inhibits purine synthesis, the citric acid cycle, and the formation of urea. Vinblastine exerts some immunosuppressive activity.

5.2 Pharmacokinetic properties

Vinblastine sulfate is unpredictably absorbed from the GI tract. Following intravenous administration, the drug is rapidly cleared from the blood and distributed into body tissues.

Vinblastine crosses the blood-brain barrier poorly and does not appear in the CSF in therapeutic concentrations. Vinblastine is reported to be extensively metabolised, primarily in the liver, to desacetylvinblastine, which is more active than the parent compound on a weight basis. The drug is excreted slowly in urine and in faeces via the bile.

5.3 Preclinical safety data

None

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Water for injections

6.2 Incompatibilities

Vinblastine sulfate is incompatible with furosemide, when injected sequentially into Y-site with no flush between or when mixed in syringe. Immediate precipitation results.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Keep vial in outer carton in order to protect from light.

6.5 Nature and contents of container

10 ml, Type I clear conventional glass vial, West Type 1888 rubber closure, aluminium spun cap ring, in packs of 5 vials.

10 ml, Type I clear Onco-Tain® vials, West Type 1888 rubber closure, aluminium spun cap ring, in packs of 5 vials.

Not all above presentations and pack sizes may be marketed.

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)

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

b) Operations such as reconstitution of powder and transfer to syringes should be carried out only in the designated area.

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

d) 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 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 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. MANUFACTURER:

Manufactured in India by:
TAJ PHARMACEUTICALS LTD.
Mumbai, India
Survey No.188/1 to 189/1,190/1 to 4,
Athiyawad, Dabhel,
Daman- 396210 (INDIA)