VINBLASTINE SULPHATE

Vinblastine Sulphate

1 mg/ml Solution for Injection

Reference Market: United Kingdom

AfME Markets using same as LPD: Saudi Arabia

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vinblastine Sulphate 1 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains 1.0 mg of vinblastine sulphate.

Each 10 ml presentation contains 10 mg of vinblastine sulphate.

Excipient with known effect

Vinblastine Sulphate 1 mg/ml solution for injection contains 35.42 mg sodium in each 10 ml vial.

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 sulphate 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 sulphate 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 sulphate, 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 mini-bag infusion 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 sulphate 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 sulphate may be completed in about one minute.

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

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

To reduce the potential for fatal medication errors due to incorrect route of administration, VinBLAStine Sulphate solution for injection should be diluted in a flexible plastic container and prominently labeled as indicated **"FOR INTRAVENOUS USE ONLY— FATAL IF GIVEN BY OTHER ROUTES"**

Mini-bags infusion 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 sulphate is contraindicated in patients who are leucopenic.

Vinblastine sulphate 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 sulphate.

4.4 Special warnings and precautions for use

Vinblastine sulphate is for intravenous use only. Vinblastine sulphate must be used only by physicians experienced in cytotoxic chemotherapy (see section 6.6).

After inadvertent intrathecal administration of vinca alkaloids, 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.

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

1. Removal of as much CSF as is safely possible through the lumbar access.

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.

Mini-bags infusion containing this product should be over labelled with the intrathecal warning label provided - **'FOR INTRAVENOUS USE ONLY. FATAL IF GIVEN BY OTHER ROUTES'.**

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 sulphate, 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. Cases of phlebitis and cellulitis have been reported.

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 dose-limiting factor is myelosuppression. In general, the larger the dose employed, the more profound and longer lasting the leucopenia will be. The fact that the granulocyte count returns to normal levels after drug-induced leucopenia is an indication that the granulocyte-producing mechanism is not permanently depressed.

Following therapy with vinblastine sulphate, the nadir in the granulocyte count may be expected to occur five to ten days after the last day of drug administration. Recovery of the granulocyte count is fairly rapid thereafter and is usually complete within another seven to fourteen days. If granulocytopenia with less than 1,000 granulocytes/mm^3 occurs following a dose of vinblastine sulphate, the patient should be watched carefully for evidence of infection until the granulocyte count has returned to a safe level. Any infection must be brought under control immediately.

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 sulphate.

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

Although the thrombocyte count is not usually significantly lowered by therapy with vinblastine sulphate, patients whose bone marrow has been recently impaired by prior therapy with radiation or with other oncolytic drugs may show thrombocytopenia (less than 150,000 platelets/mm^3). When other chemotherapy or radiation has not been employed previously, thrombocyte reduction below the level of 150,000/mm^3 is rarely encountered, even when vinblastine sulphate may be causing significant granulocytopenia. Rapid recovery from thrombocytopenia within a few days is the rule.

The effect of vinblastine sulphate upon the red blood cell count and hemoglobin is usually insignificant when other treatment does not complicate the picture.

In patients with malignant-cell infiltration of the bone marrow, the granulocyte and platelet counts have sometimes fallen drastically after moderate doses of vinblastine sulphate. Further use of the drug in such patients is inadvisable.

Breaks and aberrations were not observed on chromosome analysis of marrow cells from patients treated with vinblastine sulphate although chromosomal changes have been noted in some hamster lung cell in vitro tests.

Granulocytes and platelet counts have sometimes fallen precipitously after moderate doses of vinblastine sulphate 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 sulphate solution for injection. If accidental contamination occurs, severe irritation or corneal ulceration may result. The affected eye should be thoroughly irrigated with water immediately.

Vinblastine sulphate contains sodium
Vinblastine Sulphate contains 35.42 mg sodium in each vial, equivalent to 1.77% of the WHO maximum recommended daily intake (RDI) of 2 g sodium for an adult.

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 fatal acute respiratory distress or failure and there have been cases of pulmonary infiltration or pulmonary oedema reported.

Cases of respiratory distress with interstitial pulmonary infiltrates have been reported in patients given a regimen comprising vinblastine, mitomycin, with or without 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.

The simultaneous administration of phenytoin and anti-neoplastic chemotherapy combinations that included vinblastine 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 vinblastine sulphate.

Co-administration of cisplatin has been reported to cause higher plasma concentrations of vinblastine and severity of neutropenia may be altered when given in conjunction with cisplatin.

Following combined treatment with vinblastine, bleomycin and cisplatin, there have been reports of a decline in glomerular filtration rate which may be reversible, nephrotoxicity, pulmonary toxicity, peripheral sensory neuropathy, neurotoxicity, ototoxicity, azoospermia, irreversible high frequency hearing loss, Raynaud's phenomenon with digital ischemia and gangrene, hypertension and other vascular events (such as myocardial infarction and cerebrovascular accident).

Erythromycin may increase the toxicity of vinblastine which may cause increased severity of neutropenia, myalgia and constipation.

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

Amenorrhea has occurred in some patients treated with vinblastine sulphate in combination with other drugs. Recovery of menses was frequent.

There is no currently available evidence to indicate that vinblastine sulphate itself has been carcinogenic in humans, although some patients have developed leukaemia following radiation therapy and the administration of vinblastine sulphate in combination with alkylating agents.

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 sulphate 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

Women of childbearing potential/contraception in males and females
Women of childbearing potential should be advised to avoid becoming pregnant while receiving vinblastine sulphate. 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 6 months following last dose of vinblastine sulphate.

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 3 months following the last dose of vinblastine sulphate.

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. If 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.
Based on clinical reports, male and female fertility may be compromised. Aspermia has been reported in men. Sperm abnormalities have been noticed in mice.
Additional studies in mice demonstrated no reduction in fertility in males. It is recommended to discuss fertility preservation with men and women prior to treatment.

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, the mother should be advised not to breast-feed during the entire vinblastine sulphate therapy and for 1 week following last dose of treatment. Alternatively, a decision should be made whether to discontinue treatment with vinblastine sulphate, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

The effect of vinblastine sulphate on the ability to drive or use machines has not been systematically evaluated.

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 sulphate 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.

The frequency grouping is defined using the following convention: Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations	
Not known	Pharyngitis
Neoplasms benign, malignant and unspecified (incl. cysts and polys)	
Not known	Tumour pain
Blood and lymphatic system disorders	
Not known	Neutropenia, Leucopenia[a], Thrombocytopenia, Anaemia
Endocrine disorders	
Not known	Inappropriate anti-diuretic hormone secretion[b]
Metabolism and nutrition disorders	
Not known	Anorexia
Psychiatric disorders:	
Not known	Depression
Nervous system disorders	
Not known	Cerebrovascular accident[c] Convulsions, Numbness, Neuropathy peripheral, Loss of deep tendon reflexes, Paraesthesia Headache, Dizziness
Ear and labyrinth disorders	
Not known	VIIIth nerve injury[d]
Cardiac disorders	
Not known	Myocardial infarction[c]
Vascular disorders	
Not known	Hypertension, Raynaud's phenomenon[e]
Respiratory, thoracic and mediastinal disorders	
Not known	Dyspnoea[f], Acute respiratory distress[f]
Gastrointestinal disorders	
Not known	Haemorrhagic enterocolitis, Rectal bleeding, Peptic ulcer haemorrhage, Ileus, Nausea[g], Vomiting[g], Constipation, Oral mucosal blistering, Diarrhoea, Abdominal pain, Stomatitis
Skin and subcutaneous tissue disorders:	
Not known	Blister, Alopecia[h]
Musculosketetal and connective tissue disorders	

Not known	Myalgia, **B**one pain, Jaw pain
Reproductive system and breast disorders	
Not known	Aspermia
General disorders and administration site conditions	
Not known	Injection site phlebitis, Injection site cellulitis (and in extreme cases skin exfoliation), Extravasation, Malaise, Asthenia

[a] Leucopoenia is the most common side effect and dose limiting factor.
[b] Syndrome of inappropriate ADH secretion has been reported with higher than recommended doses.
[c] In combination chemotherapy with vinblastine sulphate, bleomycin and cisplatin.
[d] 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 sulphate is used in combination with other agents known to be ototoxic, such as the platinum-containing oncolytics.
[e] Raynaud's phenomenon has occurred when patients are being treated with vinblastine in combination with bleomycin and cisplatin for testicular cancer.
[f] reported when vinblastine is given in combinations with mitomycin (see section 4.5).
[g] antiemetics may be used to control nausea and vomiting.
[h] usually not total and in some cases the hair regrows during maintenance therapy).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after marketing 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 according to their local requirements.

To report any side effect:

- **Saudi Arabia**

National Pharmacovigilance Centre (NPC)
- Call center: 19999
- E-mail: npc.drug@sfda.gov.sa
- Website: https://ade.sfda.gov.sa/

- **Other GCC States**

- *Please contact the relevant competent authority.*

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. Any dose that results in elimination of platelets and neutrophils from blood and marrow and their precursors from marrow is life-threatening.

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

In addition, neurotoxicity similar to that seen with vincristine sulphate 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 and assessing the risk of infection.

There is no specific antidote. The use of folinic acid in addition to the other supportive measures recommended may be considered, although, unlike vincristine sulphate, studies have not been conducted to confirm its protective action.
There is no information regarding the effectiveness of dialysis nor of cholestyramine for the treatment of overdose.

Vinblastine sulphate in the dry state is irregularly and unpredictably absorbed from the gastro-intestinal tract following oral administration. Absorption of the solution has not been studied. If vinblastine sulphate is swallowed, activated charcoal in a water slurry may be given by mouth along with a cathartic. The use of cholestyramine in this situation has not been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vinca alkaloids and analogues, ATC code: L01CA01

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 sulphate 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 desacetyl vinblastine, 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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections

6.2 Incompatibilities

Vinblastine sulphate is incompatible with furosemide, when injected sequentially into Y-site with no flush between or when mixed in mini-bag infusion. Immediate precipitation results.

6.3 Shelf life

2 years.

Do not use Vincristine sulphate after the expiry date which is stated on the Vial label after EXP: The expiry date refers to the last day of that month.

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.

From a microbiological point of view, the diluted 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 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

10 ml, Type I clear conventional glass vial, rubber closure, aluminium seal with plastic flip-off top, in packs of 5 vials.

10 ml, Type I clear Onco-Tain® vials, rubber closure, aluminium seal with plastic flip-off top, 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

Keep out of the sight and reach of children.

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 mini-bags infusion 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

Mini-bags infusion, 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

MARKETING AUTHORISATION HOLDER
Hospira UK Limited,
United Kingdom

MANUFACTURER
Hospira Australia Pty Ltd,
Australia

8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14-Oct-1997

9. DATE OF REVISION OF THE TEXT

August 2024