TEVA HOSPITALS

Package leaflet: Information for the user

Vincristine sulfate, solution for injection 1 mg/ml

vincristine sulfate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1 What Vincristine sulfate is and what it is used for

Vincristine sulfate belongs to a group of medicines called anti-mitotic cytostatics. These medicines inhibit the growth of cancer cells.

Vincristine sulfate is usually used together with other medicines to treat:
- acute lymphocytic leukaemia, which is a fast-growing cancer in which the body produces a large number of immature white blood cells
- Hodgkin's disease, which is a cancer of the lymphatic vessel system
- non-Hodgkin's lymphoma, which is a cancer of the lymph nodes not due to Hodgkin's disease
- lung cancer (small cell)
- rhabdomyosarcoma, which is a cancer of the muscles
- Ewing's sarcoma, which is a type of bone cancer
- haematomas (internal bleeding) with reduced number of platelets (idiopathic thrombocytopenic purpura)
- cancer of the adrenal medulla (part of the adrenal gland)
- primitive neuro-ectodermal tumour, which is a cancer of part of the nervous system
- Wilms' tumour, which is a type of kidney cancer
- breast cancer that has spread to other parts of the body
- multiple myeloma, which is a cancer of cells of the immune system
- retinoblastoma, which is a type of cancer of the eye.

2 What you need to know before you use Vincristine sulfate

Do not use Vincristine sulfate if:
- you are allergic to vincristine sulfate or any of the other ingredients of this medicine (listed in section 6)
- you suffer from a disorder of the nerves and muscles called Charcot-Marie-Tooth syndrome
- your liver function is severely impaired
- you are suffering from constipation or are at risk of blockage of the intestines (ileus), especially in children
- you are being treated with radiotherapy on your liver.

Warnings and precautions
Vincristine sulfate should only be used under strict supervision of doctors experienced in the treatment with cytostatics (medicines to treat cancer).

Vincristine sulfate should only be administered intravenously (via the vein) and not by any other route. Other routes of administration may be fatal.

Care should be taken to avoid leakage into surrounding tissue (extravasation) as this may cause considerable irritation. The injection must be discontinued immediately.

You should avoid contact of vincristine sulfate with the eyes. If vincristine does get in the eye, you should immediately flush the eyes with a lot of water and consult your doctor if irritation persists.

In case of accidental skin contact, wash with plenty of water, then with a mild soap and rinse again thoroughly.

Talk to your doctor or pharmacist before using Vincristine sulfate:
- if you suffer from disorders of the nervous system
- if your liver does not function very well, see also section "Dosage and method of use"
- if you are taking any medicines that can be harmful to the nervous system; your doctor will monitor you carefully during treatment
- if you become constipated due to the treatment; your doctor will take measures to prevent constipation, such as an adjusted diet or the use of products that improve bowel movements (laxatives, in particular lactulose)
- if you suffer from cardiac disorders such as ischaemic heart disorders (heart and blood circulation problems)
- if you have or develop an infection; tell your doctor if this happens
- if you are sexually active; during the treatment and for 6 months after the discontinuation of the treatment both you and your partner should take precautions to prevent pregnancy.

Your doctor will perform tests to check your hepatic and renal functions, blood cell count and neurological functions before starting therapy and during treatment, and before each course of treatment. Based on the results it may be necessary to lower the dose or to pause or stop treatment.

Other medicines and Vincristine sulfate

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

An interaction can occur when this medicine is used together with:
- certain medicines that inhibit liver enzymes, for example ritonavir (used to treat HIV), nelfinavir (used to treat HIV), ketoconazole (used to treat fungal infections), itraconazole (used to treat fungal infections), erythromycin (used to treat infections) and nefazodone (used to treat depression); administration at the same time with vincristine can lead to a premature and/or increased severity of muscle diseases
- certain medicines to treat high blood pressure, for example nifedipine; the amount of vincristine in the blood may increase. This in turn, may cause more side effects
- certain medicines to treat epilepsy, for example, (fos)phenytoin; vincristine can lower the amount of phenytoin in the blood
- certain medicines to treat cancer and other bone marrow inhibiting medicines such as doxorubicin (especially in combination with prednisone); the effect, side effects and inhibiting effects on the bone marrow can be increased
- certain medicines that may be harmful to the nervous system such as isoniazid (a medicine to treat tuberculosis), L-asparaginase (a medicine to treat blood cancer) and cyclosporin A (a medicine that suppresses the immune system); these products can possibly increase the harmful effects of vincristine on the nervous system
- vaccines (vaccinations); vincristine suppresses the immune system of the body and may have an effect on the ability of the body to react to the vaccine
- digoxin (a medicine to treat reduced cardiac function and cardiac arrhythmias); vincristine can reduce the effect of digoxin
- mitomycin C (a medicine to treat certain forms of cancer); administration at the same time can cause problems with your breathing
- radiotherapy (treatment of diseases with the aid of radiation); radiotherapy can increase the side effects of vincristine on the nervous system
- ciclosporine, tacrolimus; when used at the same time your immune system may not be able to protect the body from disease (immunosuppression) with the risk of growth of certain cells (lymphoproliferation)
- GM-CSF and G-CSF (medicines used to stimulate the growth of blood cells after chemotherapy); when used at the same time this may cause a disease of the nerves (neuropathy)
- dactinomycin; in patients with kidney cancer (Wilm's tumour) severe damage to the liver has been reported
- bleomycin; this combination can cause a condition that affects blood flow to the extremities which include the fingers, toes, nose and ears when exposed to temperature changes or stress (Raynaud's syndrome).
- azole antifungals (a group of medicines used to treat fungal infections e.g. itraconazole, posaconazole, fluconazole, isavuconazole or voriconazole); side effects of vincristine may get worse.
- ketoconazole (used to treat Cushing's syndrome, a disease characterised by an excess production of the hormone cortisol); side effects of vincristine may get worse.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy
- Treatment with vincristine is not recommended during pregnancy.
- Contraceptive measures should be taken by both men and women during the treatment and for 6 months after you finish your treatment.
- As soon as you suspect a pregnancy or if you wish to have children, you should consult your doctor.
- There are no adequate data about the use of vincristine sulfate during human pregnancy to determine the possible harmful affects. This medicine has appeared harmful in animal tests.

Breast-feeding
- DO NOT breast-feed while you are being treated with Vincristine Sulfate.

Fertility
- Vincristine may have an *anti-fertility effect*, which could be irreversible. Male patients are therefore advised not to father a child either during treatment, or for 6 months after treatment, and to seek advice on storing of sperm ("sperm banking") prior to treatment.

Driving and using machines
- Treatment with Vincristine sulfate can sometimes result in side effects of the nervous system, such as reduced reflexes, muscle weakness and visual problems and of the gastrointestinal tract (see "Possible side effects"). If you experience any of these side effects, DO NOT drive or use any machines that require your attention.

Vincristine sulfate contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially "sodium-free".

3 How to use Vincristine sulfate

Follow the advice of your doctor carefully when using Vincristine sulfate. Consult your doctor or pharmacist if there is anything that you are not sure about.
Consult your doctor if you have the feeling that Vincristine sulfate is acting too strongly or not strongly enough.

Vincristine should be given only into a vein (intravenously).

The recommended dose is

- **Adults**
  The usual dose in adults is 1.4 mg per square metre of body surface (the size of your body) (maximum of 2 mg) once a week.
- **Children**
  For children who weigh more than 10 kg

the usual dose is 1.5-2.0 mg per square metre of body surface once a week. For children who weigh 10 kg or less, the starting dose is 0.05 mg per kg of body weight once a week.
Note: In infants the dose is calculated according to individual body weight (not according to body surface area).

- **Patients with a reduced liver function**
  If your liver is not working well, your doctor will adjust your dose if necessary.

Method of use

Vincristine sulfate is injected by means of an infusion or as a slow injection through the tube of a running infusion into a vein (intravenous). Vincristine should only be used under strict supervision of doctors experienced in the treatment with cytotoxic medicines.

If you have received more Vincristine sulfate than you should

If you are concerned that you have received too much Vincristine sulfate, contact your doctor or pharmacist immediately.
If you have received too much Vincristine sulfate, the described side effects may be experienced more strongly or with more serious effects.
There is no effective treatment for a Vincristine overdose. In case of an overdose your doctor will take supportive measures and monitor you carefully.

If you have missed a dose of Vincristine sulfate
Your doctor will decide when you will receive this medicine. If you think you have missed a dose, please contact your doctor as soon as possible.

If you have any further questions on the use of this medicines, ask your doctor or pharmacist.

4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Side effects may be pronounced in patients with hepatic impairment.

The following side effects may occur at the approximate frequencies shown:

Very common (may affect more than 1 in 10 people)
Common (may affect up to 1 in 10 people)
Uncommon (may affect up to 1 in 100 people)
Rare (may affect up to1 in 1,000 people)
Very rare (may affect up to 1 in 10,000 patients)
Not known (frequency cannot be estimated from the available data)

Immune system
- **Rare**
  Hypersensitivity reaction with a large drop in blood pressure, paleness, restlessness, weak rapid pulse, clammy skin and reduced consciousness (anaphylaxis), rash and fluid accumulation.

Blood
- **Common**
  Temporary increase in the number of platelets; you may experience headache, dizziness, tingling hands, fingers or feet, a blue coloured nose, bruises or bleeding gums.
- **Uncommon**
  Inhibition of bone marrow function, blood deviations such as anaemia (you may experience weakness, fatigue and/or general malaise), shortage of white blood cells (which is associated with an increased risk of infections) and shortage of platelets (you may experience bruising and bleeding tendencies).

Nervous system
- **Common**
  Peripheral neuropathy, which involves damage to the peripheral nervous system (PNS), the nerves that carry electrical signals from the brain and spinal cord to the rest of the body and back again. It can affect movement, sensation and bodily functions; you may experience effects such as sensory disturbances, observations of tickling, itching or tingling without cause, nerve pain (amongst others in the jaw or testicles), problems with moving, loss of certain reflexes (deep tendon reflexes), paralysis or weakness of muscles of the foot (foot drop), muscle weakness, coordination problems (for instance, walking as if drunk) and paralysis. The cranial nerve (brain nerve) may be affected, which may lead to paralysis of certain muscles, muscle weakness of the larynx, hoarseness, paralysis of the vocal cord, muscle weakness of the outer eye muscles, drooping of the eyelids (ptosis), double vision, disorders of the ocular nerves, disorders of the nerves outside the eye, (transient) blindness.
- **Uncommon**
  Seizures/convulsions, often with increased blood pressure. A few cases of seizures followed by coma in children have been reported. Altered consciousness and mental changes such as depression, agitation, sleeplessness, confusion, severe mental illness in which control over behaviour and actions is disturbed (psychoses), observations of things that are not there (hallucinations).
- **Not known**
  Disease occurring in the white matter of the brain (leukoencephalopathy). Symptoms include mental dysfunction and convulsions

Heart
- **Uncommon**
  In some patients, who were treated with vincristine in combination with other products to treat cancer and who were previously irradiated in the area around the heart, disorders of the blood vessels of the heart and heart attacks have occurred.
- **Rare**
  Increased blood pressure or reduced blood pressure.

Respiratory system
- **Common**
  Suddenly occurring shortness of breath and breathlessness due to cramp of the muscles of the airways (bronchospasm), especially if the medicine is used at the same time as mitomycin C.

Gastrointestinal system
- **Common**
  Constipation, abdominal pain, attack of pain in the abdomen due to a cramping of amongst others the intestines and biliary system (organs and ducts (bile ducts, gallbladder and associated structures) that are involved in the production and transportation of bile) (colic-like abdominal pains), nausea, vomiting.
- **Uncommon**
  Lack of appetite, weight loss, diarrhoea, reduced effect of the intestine due to paralysis (paralytic ileus, in which the bowel ceases to function and there is no peristalsis) especially in young children.
- **Rare**
  Inflammation of the mucous membrane of the mouth, dying off of tissue in the small intestine and/or the occurrence of damages in the wall of the intestine.
- **Very rare**
  Inflammation of the pancreas (pancreatitis).

Liver or bile
- **Rare**
  Liver disorder as a result of vein closures in the liver, particularly in children.

Skin
- **Very common**
  Hair loss (reversible after treatment is stopped).

Ears and organs of balance
- **Uncommon**
  Deafness.

Kidneys and urinary tract
Elderly patients who also use medicines that cause the lack of ability to urinate (urinary retention) must stop using these medicines soon after the vincristine administration
- **Uncommon**
  Problems with urinating (painful, urinate often or not being able to urinate well). Presence of high levels of a certain breakdown product (uric acid) in the blood, (hyperuricaemia).
- **Rare**
  Inappropriate release of Antidiuretic hormone (ADH), resulting in low blood pressure, dehydration, abnormal levels of nitrogen-containing compounds (you may experience a dry mouth, confusion, fatigue), fluid retention, which may result in oedema and sodium shortage (Syndrome of inappropriate antidiuretic hormone secretion (SIADH)).
- **Very rare**
  Incontinence

Sexual organs
Irreversible infertility is more common in males than in females.
- **Common**
  Shortage of semen, nerve pain in the testicles.
- **Uncommon**
  Stopping of the menstruation.

Other
Treatment related cancer. In some patients who have been treated with vincristine in combination with other products to treat cancer, a different form of cancer occurred after the treatment.
- **Common**
  Irritation at the place of injection.
- **Uncommon**
  Pain and inflammation of the veins and the subcutaneous connective tissue during injection into the vein, fever.
- **Rare**
  Headache.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App store. By reporting side effects you can help provide more information on the safety of this medicine.

5 How to store Vincristine sulfate

Keep this medicine out of the sight and reach of children.

Store in a refrigerator (2°C – 8°C).
Keep container in the outer carton in order to protect from light.

Do not use Vincristine sulfate after the expiry date which is stated on the vial label and carton after "EXP". The expiry date refers to the last day of that month.

Do not use Vincristine sulfate if you notice that the solution is not clear and colourless or slightly yellow.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6 Contents of the pack and other information

What Vincristine sulfate contains
The active substance is vincristine sulfate, 1 mg per ml injection fluid.
The other ingredients are mannitol, sulfuric acid and/or sodium hydroxide and water for injections.

What Vincristine sulfate looks like and contents of the pack
Vincristine sulfate is a clear, colourless or slightly yellow solution, free of particles other than gas bubbles.

Pack sizes
1 vial of 1 ml containing 1 mg vincristine sulfate
1 vial of 2 ml containing 2 mg vincristine sulfate
1 vial of 5 ml containing 5 mg vincristine sulfate

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

Teva UK Limited
Ridings Point, Whistler Drive,
Castleford, WF10 5HX, United Kingdom

Manufacturer

Pharmachemie B.V.
Swensweg 5, P.O. Box 552
2003 RN Haarlem, the Netherlands

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PREPARATION GUIDE FOR USE WITH VINCRISTINE SULFATE, SOLUTION FOR INJECTION 1MG/ML

(Please note this is a Prescriber Information Leaflet NOT the SPC. For full details regarding this product please refer to the SPC.)

The following information is intended for medical or healthcare professionals only:

1. NAME OF THE MEDICINAL PRODUCT

Vincristine sulfate, solution for injection 1 mg/ml.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of 1 ml contains 1 mg of Vincristine sulfate.
Each vial of 2 ml contains 2 mg of Vincristine sulfate.
Each vial of 5 ml contains 5 mg of Vincristine sulfate.

1 ml of solution contains 1 mg vincristine sulfate

For a full list of excipients, see section 5.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear colourless solution or slightly yellow solution, free of particles other than gas bubbles.
The pH is 3.5 – 5.5 and osmolality is approximately 600 mOsm/l.

4 Posology and method of administration

VINCRISTINE SULFATE SHOULD ONLY BE ADMINISTERED INTRAVENOUSLY. FATAL IF GIVEN BY OTHER ROUTES

Posology
Extreme care must be used in calculating and administering the dose to be injected, because overdose can have severe and even fatal results. When used as monotherapy, the dose should be administered at 1 week intervals. In combination with other antineoplastic agents, the dosing frequency depends on the protocol.
The usual dose for adults is 1.4 mg/m² (maximum of 2 mg) once a week.
Children can tolerate a higher dose: 1.5-2.0 mg/m² once per week. For children weighing 10 kg or less, the usual starting dose is 0.05 mg/kg once a week.

Elderly

The normal adult dose is still appropriate in the elderly

Hepatic impairment
In patients with hepatic impairment or with a direct serum bilirubin value above 3 mg/100 ml a reduction of 50% of the dose of vincristine sulfate is recommended. 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.

In case of severe neurotoxicity, vincristine sulfate should not be administered, particularly in case of paresis. When the complaints decrease after discontinuation of the administration of vincristine sulfate, the treatment may be resumed with 50% of the dose.

Method of administration
Vincristine sulfate should only be used under strict supervision of physicians experienced in the treatment with cytotoxic products.

Intrathecal administration of vincristine results in fatal neurotoxicity. Vincristine sulfate can be administered intravenously via an infusion or as a bolus injection of at least 1 minute via the line of a running infusion.
Caution: it is extremely important that the needle be properly positioned in the vein before any drug is injected.
Care should be taken to avoid infiltration of subcutaneous tissues. Extravasation during intravenous administration of vincristine sulfate can cause considerable irritation. In order to prevent vascular irritation, the vein should be flushed well after the administration of vincristine sulfate.
The dose of vincristine sulfate should be calculated and administered with extreme care, because overdose can have severe and even fatal results.

The dose should not be increased beyond the level which produces therapeutic benefit. In general, individual doses should not exceed 2 mg; and white cell counts should be carried out before and after giving each dose

5 List of excipients

Mannitol.
Sulfuric acid (for pH adjustment).
Sodium hydroxide (for pH adjustment).
Water for injections.

6 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

7 Shelf life

Vial before opening

24 months

After dilution
Chemical and physical in-use stability of the solution prepared for injection or infusion has been demonstrated for 48 hours at 2-8 ° C or 24 hours at 15 to 25 °C when diluted to a concentration range of 0.01 mg/ml to 0.1 mg/ml in 9 mg/ml (0.9%) sodium chloride solution for infusion or in 50 mg/ml (5%) glucose solution for infusion.
From a microbiological point of view, the diluted solution 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

8 Special precautions for storage

Store and transport refrigerated (2-8°C). Keep vial in the outer carton in order to protect from light.

9 Nature and contents of container

Colourless Type I glass vial with bromobutyl rubber stopper, aluminium seal and polypropylene snap-cap containing 1 ml,
2 ml or 5 ml of solution.

Pack sizes:
One vial containing 1 ml of solution.
One vial containing 2 ml of solution.
One vial containing 5 ml of solution.

Not all pack sizes may be marketed

10 Special precautions for disposal <and other handling>

Inspection prior to use
Only clear solutions without particles should be used. The product should not be used in case of a defective container.

Handling and disposal
Injectable solutions of cytotoxic drugs should be prepared by specialized trained personnel who are familiar with the drugs used, under conditions that guarantee environmental protection and especially protection of personnel handling the drugs. Vincristine should not be handled by pregnant staff.

Any contact with the liquid should be avoided. The solutions should be prepared in a special area in which smoking, eating and drinking are prohibited. During the preparation a strictly aseptical work technique must be applied; as protective measures the use of gloves, mouth mask, safety goggles and protective clothing are needed. The use of a LAF-cabinet with vertical flow direction is recommended. During administration gloves should be worn. With waste processing, the nature of this product should be taken into account.

If the solution does get in contact with the skin, mucous membranes or eyes, immediate excessive flushing with water should occur.

Extravasation should be avoided. Should extravasation occur, the injection should be stopped immediately and any remaining dose should be injected in a different vein. Local injection of hyaluronidase 250 IU/mL (1 mL subcutaneous around the lesion and moderate heat application at the site where the extravasation occurred, can help disperse the product and limit the discomfort and possible cellulitis to a minimum. In the unit where vincristine sulfate is administered, the hospital's cytostatics extravasation set of the hospital should be available.

Excreta and vomitus should be handled with caution.
Broken containers should be handled with the same precautions and treated as contaminated waste. Contaminated waste should be disposed of by incineration in rigid, appropriately labelled containers.