SUMMARY OF PRODUCT CHARACTERISTICS

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 the full list of excipients, see section 6.1.

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. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vincristine sulfate is used either alone or in conjunction with other oncolytic drugs for the treatment of:

1. Acute lymphocytic leukaemia
2. Malignant lymphomas, including Hodgkin's disease and non-Hodgkins lymphomas
3. Multiple myeloma
4. Solid tumours, including (metastatic) breast carcinoma, small cell lung carcinoma
5. Ewing's sarcoma, embryonal rhabdomyosarcoma, primitive neuro-ectodermal tumours (such as medulloblastoma and neuroblastoma), Wilm's tumour and retinoblastoma
6. Idiopathic thrombocytopenic purpura. Patients with true ITP refractory to splenectomy and short-term treatment to 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 result with the additional doses.

4.2 Posology and method of administration

VINCRISTINE SULFATE SHOULD ONLY BE ADMINISTRED INTRAVENOUSLY. FATAL IF GIVEN BY OTHER ROUTES
See Section 4.4 Special warning and precautions for use.

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 is:

Adults
For adults the usual dose is 1.4 mg/m² (maximum of 2 mg) once a week.

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 giving each dose.

Paediatric population
Children can tolerate a higher dose: For children weighing more than 10 kg, the usual dose is 1.5-2.0 mg/m² once a week.

For children weighing 10 kg or less, the usual starting dose is 0.05 mg/kg once a week.

Note: In infants the dose is calculated according to individual body weight (not according to body surface area). The ratio between body surface area and body weight is unfavorable in infants and pronounced neurological and hepatic side effects can occur after chemotherapy for acute leukemia, compared to older children.

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 (51 μmol/l) 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 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 (see section 4.4). In order to prevent vascular irritation, the vein should be flushed well after the administration of vincristine sulfate.

4.3 Contraindications

Vincristine sulfate is contra-indicated in patients with:
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- neuromuscular disorders (such as the demyelinating form of Charcot-Marie-Tooth syndrome);
- a severe liver function disorder;
- constipation and impending ileus, especially in children;
- radiotherapy in which the liver is involved.

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

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

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

Accidental intrathecal administration
After inadvertent intrathecal administration, immediate neurosurgical intervention is required in order to prevent ascending paralysis leading to death.
In a very small number of patients, life-threatening paralysis and subsequent death was averted but resulted in devastating neurological sequelae, with limited recovery afterwards.

Based on the published management of these survival cases, if vincristine 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.

Contact with the skin and the mucous membranes
Care should be taken to avoid contact of vincristine sulfate with the eyes. This can result in severe irritation or ulcer formation of the cornea (especially if the medicinal product is administered under pressure). When contact with the eyes occurs, the eyes must be flushed immediately with large quantities of water. Patients should consult a physician or ophthalmologist if the irritation of the eyes persists.
In the event of accidental projection on the skin, wash abundantly with water then with a mild soap and rinse thoroughly.

Extravasation
Extravasation should be avoided. Should extravasation occur, the injection should be stopped immediately and the possible 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 extravasation occurred can help disperse the drug and limit the discomfort and possible cellulitis to a minimum. In the unit where vincristine sulfate is administered, the hospital’s cytostatics extravasation set should be available.

Myelotoxicity
Since leukopenia can occur, both the physician and the patient should be alert to the occurrence of an infection. When leukopenia occurs, suitable measures should be taken, amongst which a careful consideration about the time at which the next dose of

vincristine sulfate should be administered. A complete blood count should be done before administration of each dose.
Due to an increased risk of leukopenia and thrombocytopenia, closer monitoring is necessary in patients in whom previous therapy or the disease itself has suppressed bone marrow function.

Neurotoxicity
Special attention should be paid to patients with existing neurological disorders. Careful observation of the patient is required with the combined use of vincristine and pharmaceuticals with a potential neurotoxicity.

The neurotoxic effect of vincristine sulfate may be additive with other neurotoxic agents or increased by spinal cord irradiation and neurological disease. Elderly patients may be more susceptible to the neurotoxic effects of vincristine sulfate.

Interaction with azole antifungals
Concomitant administration of azole antifungals with vincristine has been associated with neurotoxicity and other serious adverse reactions, including seizures, peripheral neuropathy, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and paralytic ileus.
Reserve azole antifungals for patients receiving vincristine who have no alternative antifungal treatment options (see section 4.5).

Hepatic impairment
Hepatic dysfunction may increase the circulating concentrations and the plasma half-life of vincristine with an increase in its adverse effects because vincristine is predominantly metabolised in the liver.
Vincristine should not be given to patients receiving radiotherapy if the radiation field includes the liver.
Hepatic and renal functions, blood cell count and neurological functions should be assessed before starting therapy and during treatment, and before each course of treatment. If there are signs of bone marrow depression, the next dose should only be given after careful assessment of the clinical picture. The same applies to the occurrence of neurological symptoms, as severe neuropathies may develop if treatment is continued.

Patients who received vincristine chemotherapy in combination with anticancer drugs known to be carcinogenic have developed secondary malignancies. The contributing role of vincristine in this development has not been determined.
Prophylactic measures for the prevention of constipation, such as an adjusted diet and the use of laxatives, in particular lactulose, are recommended.

Vincristine should be administered with caution to patients with ischaemic heart disorders.

Acute elevation of the serum uric acid level can occur during the remission-induction of acute leukaemia; therefore the serum uric acid levels should be frequently determined

during the first 3-4 weeks of the treatment or suitable measures should be taken to prevent uric acid neuropathy.

Contraceptive measures should be taken by both the male and the female patients during the treatment and for 6 months after discontinuation of the treatment (also see section 4.6).

Excipient(s)

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘‘sodium-free’’.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions common to all cytotoxics
Due to the increase of thrombotic risk in case of malignancies, the use of anticoagulative treatment is frequent. The high intra-individual variability of the coagulability during diseases, and the eventuality of interaction between oral anticoagulants and anticancer chemotherapy require, if it is decided to treat the patient with oral vitamin K antagonists, to increase frequency of the INR (International Normalised Ratio) monitoring.

Inhibitors of cytochrome P450 isoenzymes and P-glycoprotein
Vinca alkaloids are metabolised by the cytochrome P450 3A4 iso-enzyme (CYP3A4) and are substrates for P-glycoprotein. Therefore increased plasma concentrations of vincristine can occur when CYP3A4 and P-glycoprotein inhibitors, such as for instance ritonavir, nelfinavir, ketoconazole, itraconazole, erythromycin, cyclosporine, nifedipine and nefazodone, are administered concomitantly. Concomitant administration of itraconazole and vincristine has been associated with an earlier onset and/or increased severity of neuromuscular side effects, probably related to inhibition of the vincristine metabolism.

Concomitant administration of azole antifungals (e.g., itraconazole, voriconazole, posaconazole, isavuconazole and fluconazole) with vincristine may increase the plasma concentrations of vincristine, which can lead to an early onset and/or increased severity of neurotoxicity and other side effects (see section 4.4). Therefore, azole antifungals should be used with caution in patients receiving vincristine and should only be used when there are no alternative antifungal treatment options available or when the potential benefits outweigh the risks of the combination. Patients should be closely monitored for adverse effects with concomitant use.

Nifedipine
Care should be taken regarding the possible interaction between vincristine sulfate and calcium channel blockers, especially nifedipine. Concomitant administration of vincristine sulfate and nifedipine may cause a decrease in plasma clearance of vincristine sulfate with a risk of increased toxicity.

Phenytoin and fosphenytoin

It has been reported that concomitant administration of phenytoin and anti-neoplastic chemotherapy combinations, that contain amongst others vincristine, reduce the blood levels of phenytoin and increase the proconvulsant effect. This combination is not recommended. If it cannot be avoided, adjustment of the dose should be based on the blood level determinations.

Other cytostatics
Pharmacodynamic interactions can occur with other cytostatics: potentiation of therapeutic and toxic effect. Concomitant use of vincristine and other bone marrow depressive medicinal products such as doxorubicin (especially in combination with prednisone) can potentiate the depressive effects on the bone marrow.

Asparaginase/isoniazid and other neurotoxic medicinal products
When vincristine is used in combination with L-asparaginase, vincristine should be given 12-24 hours before administration of L-asparaginase, because a decrease in hepatic clearance of vincristine sulfate may result in cumulative hepatotoxicity. Because of the neurotoxicity of vincristine sulfate, other potentially neurotoxic medicinal products, such as ciclosporin and isoniazid, should not be administered concomitantly.

Vaccines/killed virus
Because the normal immune system can be suppressed due to the treatment with vincristine, the formation of antibodies by the body may be reduced as a reaction to the vaccine. The time interval between the discontinuation of the use of the medicinal products that cause immuno-suppression and the recovery of the ability of the body to react to the vaccine is dependent on the intensity and the type of the immuno-suppressive products, the underlying disease and other factors; estimates vary from 3 months to 1 year.

Vaccines/live virus
Because the normal immune system can be suppressed due to the treatment with vincristine, the concomitant administration of a live virus vaccine may enhance the replication and the side effects of the virus vaccine, and/or the formation of antibodies by the body as a reaction to the vaccine may be reduced; these patients should only be immunised with the utmost caution after careful evaluation of the haematological status of the patients and only with the approval of the treating physician. The time interval between the discontinuation of the use of the medicinal products that cause immuno-suppression and the recovery of the ability of the body to react to the vaccine is dependent on the intensity and type of the immuno-suppressive products, the underlying disease, and other factors; estimates vary from 3 months to 1 year. Patients with leukaemia in remission should not receive live virus vaccine until at least 3 months after their last chemotherapy treatment.

Digoxin
The absorption of digoxin can be reduced in patients who are treated with chemotherapy. In some patients therefore the therapeutic effect of digoxin may be reduced. Therefore caution is needed when such combinations are administered and adjustment of the dose of digoxin may be needed.

Mitomycin C
Acute pulmonary reactions can occur.

Radiotherapy
Radiotherapy can enlarge the peripheral neurotoxicity of vincristine.

Ciclosporin, Tacrolimus
Excessive immunosuppression with risk of lymphoproliferation can occur.

Other
During concomitant administration of vincristine and colony-stimulating factors (G-CSF, GM-CSF) atypical neuropathies with stinging or burning sensations in distal extremities were reported more frequently.

In patients with Wilms tumour, severe liver toxicity was reported under the combination of vincristine and dactinomycin.

In combination with bleomycin, vincristine can cause Raynaud syndrome in a dose-dependent manner.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is very limited amount of data from the use of vincristine in pregnant patients. Studies in animals have shown teratogenicity and other reproductive toxicity (see section 5.3). Based on results from animal studies and the pharmacodynamics of the substance, vincristine should not be used during pregnancy, particularly during the first trimester. If pregnancy occurs during treatment with vincristine the patient must be informed about the possible dangers to the fetus.

Contraceptive measures should be taken by both the male and the female patients during the treatment and for 6 months after discontinuation of the treatment (also see section 4.4).
If pregnancy occurs during treatment, the patient should be informed about the risks for the unborn child and should be monitored carefully.

Vincristine can have genotoxic effects. Therefore, the possibility of genetic counselling should be considered if pregnancy occurs during therapy with vincristine and is also recommended for patients wishing to have children after therapy.

Breast-feeding
It is unknown whether vincristine is excreted in human breast milk. Breast-feeding must be discontinued during treatment with vincristine sulfate.

Fertility
Treatment with vincristine may cause irreversible infertility. The reversibility of these antifertility effects depends on the age of the patient and the dose administered.
Commonly, azoospermia has been observed in men who were treated with a chemotherapy combination consisting of vincristine and prednisone with

cyclophosphamide or mechlorethamine and procarbazine. Less commonly, amenorrhea has been observed in women who were treated with vincristine containing chemotherapy.
Patients should be consulted about future fertility prospects. Male patients have to be consulted about sperm preservation.

4.7 Effects on ability to drive and use machines

Due to the (neurological and gastrointestinal) side effects, this medicinal product may affect the ability to drive and use machines.

4.8 Undesirable effects

In general the side effects are reversible and dose dependent. The most important toxic effects of vincristine have been associated with the central nervous system. The most often occurring side effects are neurotoxicity and alopecia; the most troublesome side effects are neuromuscular in origin.

Side effects may be pronounced in patients with hepatic impairment due to reduced metabolism and delayed biliary excretion.

Side effects are listed by frequency, the most frequent first, using the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Neoplasms, benign and malignant and unspecified (including cysts and polyps)
Treatment related secondary malignancy
Patients who have been treated with vincristine in combination with other cytotoxic products, of which it is known that they are carcinogenic, have developed secondary malignancies.

Blood and lymphatic system disorders
Common
Temporary thrombocytosis.

Uncommon
Severe bone marrow depression, anaemia, leukopenia and thrombocytopenia.

Immune system disorders
Common
Acute occurrence of shortness of breath and bronchospasms, which can be severe and life threatening. These symptoms were observed after the administration of vinca alkaloids (such as vincristine), particularly when administered concomitantly with mitomycin. The reaction can occur a few minutes to hours after the administration of a vinca alkaloid or to 2 weeks after a dose of mitomycin.

Rare
Allergic reactions, such as anaphylaxis, rash and oedema, possibly related to vincristine therapy have been observed in patients who were treated with vincristine as part of multi-drug chemotherapy regimes.

Nervous system disorders
The neurological toxicity is the most important side effect of vincristine. Neurological toxicity is dose and age related. As a result of neurotoxicity also constipation and ileus can occur (see "Gastrointestinal system disorders").

Common
The most frequently occurring neurotoxic side effect is peripheral neuropathy (mixed sensorimotor), which occurs in almost all patients. Often a specific order in the development of neuromuscular side effects occurs. In the beginning only sensory disturbances and paraesthesia occur. With continuation of the treatment nerve pain (amongst other in the jaw and testicles) and further motor difficulties can occur. Loss of deep tendon reflexes, foot drop, muscle weakness, ataxia and paralysis have been reported with continuation of the treatment. Affection of the cranial nerve, amongst which isolated paresis and/or paralysis of muscles that are directed by the cranial nerves, can occur, without muscle weakness occurring anywhere else.

Paralysis of the cranial nerve and muscle weakness of the larynx can cause hoarseness and vocal cord paresis, amongst which potentially life threatening bilateral vocal cord paresis. Muscle weakness of the outer ocular muscles can cause ptosis, and optical and extra ocular neuropathy. Transient cortical blindness has been reported. Vincristine also causes autonomic toxicity and toxicity of the central nervous system, although less frequent than peripheral neuropathy. Double vision and optic atrophy are observed.

Uncommon
Convulsions, frequently with hypertension, have been reported in a few patients receiving vincristine sulfate. A few cases of convulsions followed by coma have been reported in children. Vincristine causes autonomic toxicity and toxicity of the CNS, although this occurs less frequently than peripheral neuropathy. Effects on the CNS e.g. altered state of awareness and mental changes like depression, agitation, sleeplessness, confusion, psychoses and hallucinations.

Not known
Leukoencephalopathy.

Ear and labyrinth disorders
Uncommon
Deafness.

Cardiac disorders
Uncommon
Coronary artery disease, myocardial infarction.
Coronary vascular disorders and myocardial infarction have occurred in patients who were treated with vincristine containing chemotherapy combinations and who were previously treated with radiotherapy of the mediastinum.

Rare
Hypertension and hypotension.

Respiratory, thoracic and mediastinal disorders
Common
Severe bronchospasm and dyspnea have been reported with vinca alkaloids, some of which were used in combination with mitomycin C.

Gastrointestinal disorders
Common
Nausea, vomiting, constipation, abdominal pain. Constipation can occur as a result of impaction of the upper part of the intestines while the rectum is empty. Colic-like abdominal pains can then occur.

Uncommon
Reduced appetite, weight loss, anorexia, diarrhoea, paralytic ileus. Especially in young children paralytic ileus is a possibility.

Rare
Inflammation of the mucous membrane of the mouth, intestinal necrosis and/or perforation.

Very rare
Pancreatitis.

Hepatobiliary disorders
Rare
Hepatic veno-occlusive disease, particularly in children.

Skin and subcutaneous tissue disorders
Very common
Alopecia (is reversible when the administration of vincristine is discontinued).

Renal and urinary disorders
In elderly patients the therapy with drug that causes urinary retention must be interrupted in the early days after the vincristine administration.

Uncommon
Polyuria, dysuria, urinary retention as a result of bladder atony, hyperuricaemia, uric acid nephropathy.

Rare
SIADH syndrome (syndrome of inappropriate antidiuretic hormone secretion). The syndrome may be related to the neurotoxicity of the medicinal product possibly due to a direct effect on the hypothalamus. In these patients hyponatraemia occurs, in combination with urinary sodium excretion, without indication of renal or adrenal disorders, hypotension, dehydration, azotemia or oedema. With liquid restriction the hyponatraemia and the loss of sodium through the kidneys can be improved.

Very rare

Incontinence.

Reproductive system and breast disorders
Irreversible infertility after vincristine-containing chemotherapy is more common in males than in females.

Common
Azoospermia has been observed in men who were treated with a chemotherapy combination consisting of vincristine and prednisone with cyclophosphamide or mechlorethamine and procarbazine.

Uncommon
Amenorrhea.

General disorders and administration site conditions
Common
Injection site irritation.

Uncommon
Fever, phlebitis, pain, cellulitis and necrosis. These symptoms can occur after irritation of the vessel wall or after extravasation during the administration.

Rare
Headache.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms
An overdose with vincristine leads to the occurrence of the above mentioned undesirable effects, in an intensified manner. In children younger than 13 years of age, overdose of 10 times the recommended dose has had fatal results. In this patient group, severe symptoms can occur with doses of 3-4 mg/m^2. Adults can expect severe symptoms after the administration of single doses of 3 mg/m^2 or more.
The main clinical symptoms of overdose are abdominal pain, neurotoxic effects such as areflexia, sensory and motor disturbances, somnolence, thrombocytopenia, leukopenia, and paralytic ileus.

Management
There is no known antidote to vincristine sulfate. Treatment is symptomatic and supportive. On appearance of an overdose, careful monitoring of the patient is required. The following measures should be considered.

- The serum electrolyte concentrations and fluid balance should be carefully monitored and when signs of inappropriate ADH secretion occur, fluid restriction must be initiated.
- Administration of an anti-convulsive agent for at least 1 week after overdose.
- Use of enemas to prevent ileus.
- Monitoring of the cardiovascular system.
- Monitoring of the blood, after which action should be based on the observed bone marrow depression.

- Folinate may be used. A proposed schedule is 100 mg intravenously every 3 hours for 24 hours followed by every 6 hours for at least 48 hours.

Because only very small quantities of the medicinal product end up in dialysis, haemodialysis in case of overdose is probably not effective.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agent-vinca alkaloid
ATC code: L01C A02

Vincristine sulfate is a salt of vincristine, an alkaloid obtained from the periwinkle plant Vinca rosea Linn.
Vinca alkaloids are classical “spindle poisons”, that bind to the microtubular protein tubulin and block cells during metaphase by both preventing polymerisation of tubulin and subsequent formation of microtubules and by inducing depolymerisation of existing microtubules.
Vinca alkaloids can exert their effect on the process in a number of ways:
- by binding to a specific site of tubulin and by forming a tubulin-alkaloid aggregation complex;
- by binding to a high affinity site of tubulin, incorporated into microtubeles, and by inhibition of further incorporation of tubulin into the existing microtubule;
- by binding to a low affinity site on the microtubule wall that cases protofilament separation.

Vincristine can also affect other cellular systems such as RNA and DNA synthesis, cyclic AMP, lipid biosynthesis and calmodulin-dependent Ca2+ transport ATPase.

5.2 Pharmacokinetic properties

Distribution
After the intravenous injection vincristine is rapidly cleared from the serum. Within 15-30 minutes more than 90% of the medicinal product is distributed from the serum to the tissues and other blood components. The distribution volume is 8.4 ± 3.2 l/kg during steady-state conditions.
Twenty minutes after the intravenous administration, more than 50% of vincristine is bound to blood components, particularly to platelets, which contain high concentrations of tubulin.

Penetration into the cerebrospinal fluid after an intravenous bolus injection appears to be very low. However, despite this low penetration vincristine can cause central nervous system side effects.

Biotransformation
Vincristine appears to be largely metabolised, probably in the liver by the microsomal enzyme system cytochrome P450, amongst which CYP3A.

Elimination
Analysis of plasma particulars shows that the plasma elimination of vincristine after a rapid intravenous administration can best be described as a triphasic model. The initial, mean and final half-lives are respectively 5 minutes, 2.3 hours and 85 hours (range 19-155 hours).
Plasma clearance is slow and therefore an interval of at least one week between treatment periods is needed in order to avoid cumulative toxicity.
The liver is the most important excretion organ; approximately 80% of the injected dose is excreted in the faeces and 10-20% in the urine.

Patients with liver function disorders
In patients with liver function disorders the metabolism and because of that the excretion of vincristine is probably reduced, resulting in an increased risk of toxicity. If necessary the dose should be adjusted (see sections 4.2. and 4.4).

Paediatric population
In children there is a larger inter- and intra-individual variation in the pharmacokinetic parameters such as clearance, distribution volume and elimination half-life. The plasma clearance in children is generally larger than in adults or infants, but it is not certain that the vincristine clearance is reduced with the age during the childhood.

5.3 Preclinical safety data

In preclinical studies vincristine has been shown to be teratogenic. Also, in reproduction toxicity studies in animals, adverse effects on fertility and embryo toxicity have been observed. In chronic toxicity studies adverse effects including neurotoxicity, inhibition of the spermatogenesis, myelosuppression and gastro-intestinal toxicity have been observed. In genotoxicity tests vincristine was shown to have the potential to cause chromosomal deviations, aneuploidia and polyploidia. There are no other relevant preclinical data.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 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 ^{o}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

6.4 Special precautions for storage

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

6.5 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

6.6 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 used 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 the possibly 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 the 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.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

PL 00289/1060

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15th July 2008

10. DATE OF REVISION OF THE TEXT

23/09/2024