

NAME OF THE MEDICINAL PRODUCT

Vinorelbine "Ebewe" 10 mg/ml

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

ACTIVE INGREDIENT	FORMULATION	
	10 mg/1 ml	50 mg/5 ml
vinorelbine tartrate (mg)	13.85	69.25
equivalent to vinorelbine (INN) base (mg)	10.00	50.00

For the full list of excipients, see section 6.1.

2. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Vinorelbine "Ebewe" 10 mg/ml is a clear colourless to pale yellow solution.

3. CLINICAL PARTICULARS

3.1 Therapeutic indications

For the treatment of non small cell lung cancer.

For the treatment of advanced breast cancer.

Hormone-refractory prostate cancer, especially in combination with low dose oral corticoid therapy or Estramustin.

3.2 Posology and method of administration

Strictly intravenous administration after appropriate dilution.

Intra-theal administration of vinorelbine may be fatal.

Instructions for use and handling: refer to paragraph 6.6.

It is recommended to infuse vinorelbine over 6-10 minutes after dilution in 20-50 ml of sodium chloride 9 mg/ml (0.9%) solution for injection or in glucose solution for injection 5%.

Administration should always be followed with at least 250 ml of an isotonic solution infusion to flush the vein.

Non-small cell lung cancer and advanced breast cancer

In monotherapy the usual dose given is 25-30 mg/m² once weekly.

In combination chemotherapy the usual dose (25-30 mg/m²) is usually maintained, while the frequency of administration is reduced e.g. day 1 and 5 every 3 weeks or day 1 and 8 every 3 weeks according to treatment protocol.

Hormone-resistant prostate cancer

The usual dose given is 30 mg/m² on days 1 and 8 every 3 weeks with low doses of corticosteroids everyday (i.e. hydrocortisone 40 mg/day).

Administration in the elderly

Clinical experience has not identified relevant differences among elderly patients with regard to the response rate, although greater sensitivity in some of these patients cannot be excluded. Age does not modify the pharmacokinetics of vinorelbine.

Administration in patients with liver insufficiency

The pharmacokinetics of vinorelbine is not modified in patients presenting moderate or severe liver impairment. Nevertheless as a precautionary measure a reduced dose of 20 mg/m² and close monitoring of haematological parameters is recommended in patient with severe liver impairment (refer to sections 4.4 and 5.2).

Administration in patients with renal insufficiency

Given the minor renal excretion, there is no pharmacokinetic justification for reducing the dose of vinorelbine in patients with renal insufficiency.

Administration in children

Safety and efficacy in children have not been established and administration is therefore not recommended (see section 5.1).

3.3 Contraindications

- in case of hypersensitivity to vinorelbine or other vinca alkaloids, or to any of the excipients listed in section 6.1
- in women of child-bearing potential who are not using reliable contraceptive measures (see sections 4.4 and 4.6)
- during breastfeeding (see section 4.6)
- in case of severe infections (acute or within the last 14 days)
- in case of neutropenia ($< 1500/\text{mm}^3$) or thrombocytopenia ($< 100,000/\text{mm}^3$)
- in combination with yellow fever vaccine (see section 4.5)

3.4 Special warnings and precautions for use

Warnings

For intravenous use only.

As bone marrow depression is the main risk associated with the administration of Vinorelbin "Ebewe" 10 mg/ml, close haematological monitoring necessary during treatment (determination of haemoglobin level and number of leucocytes, neutrophils and thrombocytes before each new administration).

The dose-limiting toxic effect is usually neutropenia. This effect is non-cumulative but is most pronounced between days 7 and 14 after administration, and is quickly reversible within 5-7 days. If the number of neutrophil granulocytes is below 1500/mm³ and/or the platelet count is below 100000/mm³, the treatment should be postponed until recovery (neutrophil count >1,500/mm³ and platelet count >100,000/mm³).

If the patient presents signs or symptoms suggestive of infection, a prompt investigation should be carried out.

If radiotherapy of the bone marrow-rich regions (pelvis, spine, or long bones) is performed at the same time as vinorelbine administration, increased myelotoxicity is to be expected. This risk appears to rise as larger proportions of active bone marrow ($\geq 25\%$) receive moderate to high radiation doses $\geq 40\text{Gy}$, or when notable portions of pelvic bone marrow ($\geq 45\%$) receive lower dose levels (e.g., 20Gy). The same applies to previous radiotherapy (<3 weeks) of the regions mentioned, as marrow recovery is incomplete and susceptibility to vinorelbine induced myelosuppression remains elevated.

Injection site necrosis. This effect can be limited by precise positioning of the injection needle and good flushing of the vein. Occasionally, it may be necessary to insert a central venous access.

Precautions for use

Particular caution is required in patients with a history of ischaemic heart disease (see section 4.8).

To avoid the risk of bronchospasm and dyspnoea, appropriate prophylaxis should be considered, especially in combination treatment with mitomycin C. Patients undergoing treatment with vinorelbine require immediate medical attention if they have difficulty breathing.

The pharmacokinetics of vinorelbine is not modified in patients with presenting moderate or severe liver impairment. For dose adjustment in these specific patient groups, see section 4.2.

As there is a low level of renal excretion there is no pharmacokinetic rationale for reducing the dose of vinorelbine in patients with impaired kidney function (see section 4.2).

Vinorelbin "Ebewe" should not be given concomitantly with radiotherapy if the treatment field includes the liver.

This product is specifically contraindicated for simultaneous use with yellow fever vaccine. Concomitant use with live attenuated vaccines is not recommended.

Caution should be exercised when combining vinorelbine with strong inhibitors or inducers of CYP3A4 (see section 4.5). Its combination with phenytoin (like all cytostatics) and with itraconazole (like all vinca alkaloids) is not recommended.

Vinorelbin must not get into contact with the eye; there is a risk of severe irritation and even corneal ulceration if the drug is sprayed under pressure. If this occurs, the eye should be rinsed immediately with physiological saline solution (0.9% NaCl solution) and an ophthalmologist should be contacted.

Neurological investigations (including EMG if necessary) should be carried out during ongoing treatment with Vinorelbine or in patients with increased risk.

Treatment can be continued after normalisation of intestinal activity following the occurrence of paralytic ileus.

Antiemetic therapy is recommended due to the very frequent occurrence of nausea and vomiting.

Pulmonary toxicity, including dyspnoea, severe acute bronchospasm, interstitial lung disease (including interstitial pneumonitis), and acute respiratory distress syndrome (ARDS), has been reported with vinorelbine, predominantly with the intravenous formulation. The median time to onset of ARDS after vinorelbine administration was one week (range 3 to 8 days). The infusion must be immediately interrupted in patients who develop unclear dyspnoea or have any evidence of pulmonary toxicity.

Interstitial lung disease has been reported more frequently in the Japanese population. Special attention should be exercised for this specific population.

For information on pregnancy, breastfeeding and fertility, see section 4.6.

3.5 Interactions with other medicinal products and other forms of interactions

Interactions that can occur with all cytotoxic medicinal products:

Due to the increase of thrombotic risk in patients with cancer, the use of anticoagulant therapy is frequently necessary. The high intra-individual variability of coagulability during the course of disease and the eventuality of interaction between oral anticoagulants and anticancer chemotherapy requires to increase the frequency of the INR (International Normalised Ratio) monitoring if the patient is treated with oral anticoagulants.

Concomitant uses contraindicated:

The concomitant use of yellow fever vaccine is contraindicated due to the risk of fatal vaccinal-induced disease (see section 4.3).

Concomitant uses not recommended:

Live attenuated vaccines:

The simultaneous use of live attenuated vaccines is not recommended (for yellow fever vaccine, see concomitant use contraindicated), as there is a risk of a potentially fatal vaccine-induced disease. This risk is increased in patients who are already immunosuppressed by their underlying disease. In this case, it is recommended to use an inactivated vaccine (e.g. poliomyelitis) (see section 4.4).

Phenytoin: There is the risk of a renewed worsening of seizures resulting from a decreased concentration of phenytoin, as the absorption of phenytoin is reduced by the cytotoxic medicinal product. There is also a risk of loss of efficacy of the cytostatic medicinal product, vinorelbine, as hepatic metabolism is increased by phenytoin.

Concomitant uses to be carefully considered:

Simultaneous use of cyclosporine and tacrolimus must be carefully considered, as there may be excessive immunosuppression with the risk of lymphoproliferation.

Interactions that can occur specifically to with vinca alkaloids:

Concomitant use not recommended:

Itraconazole: Concomitant use is not recommended, as the neurotoxicity of vinca alkaloids increases due to their slower hepatic metabolism.

Concomitant use to be carefully considered:

Mitomycin C: The concomitant of mitomycin C must be carefully considered, as there is an increased risk of dyspnoea and bronchospasms. In rare case an interstitial pneumonitis was observed..

Vinca alkaloids are substrates for P-glycoprotein. Although no specific studies are available, caution should be exercised when combining vinorelbine with strong modulators of this membrane transporter(e.g. ritonavir, clarithromycin, ciclosporine, verapamil, quinidine or, among others, CYP3A4 inducers).

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Interactions that can occur specifically with to vinorelbine::

- If vinorelbine is combined with other substances with known bone marrow toxicity, an increase in the myelosuppressive effect must be expected.
- CYP3A4 is the main enzyme involved in the metabolism of vinorelbine, and the combination with an agent that induces this isoenzyme (such as phenytoin, phenobarbital, rifampicin, carbamazepine, Hypericum perforatum) or inhibits (such as itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin, nefazodone), can decrease or increase the concentration of vinorelbine in the blood(see section 4.4).
- The combination of vinorelbine and cisplatin over several cycles of treatment shows no pharmacokinetic interactions. However, a higher incidence of granulocytopenia has been reported in patients receiving combination therapy with vinorelbine and cisplatin than in those receiving vinorelbine alone.

In a clinical phase I study with intravenous vinorelbine in combination with lapatinib, an increased incidence of grade 3/4 neutropenia was observed. In this study, the recommended dose of the intravenous form of vinorelbine in a 3-week-schedule was 22.5 mg/m² on day 1 and day 8 when combined with 1000 mg of lapatinib daily. This type of combination should be administered with caution.

There is evidence that 5-fluorouracil-induced mucosal toxicity may be enhanced by vinorelbine, particularly when 5-fluorouracil is used at high doses and as a continuous infusion in combination with folinic acid. The combination of high-dose vinorelbine with mitomycin C appears to lead to signs of increased pulmonary toxicity (bronchospasms, dyspnoea) in individual cases, for which an allergic genesis is being discussed. Particular caution is advised when using vinorelbine and mitomycin C together in patients with an

allergic predisposition (bronchial asthma, known allergies).

3.6 Fertility, pregnancy and lactation

Pregnancy

There are insufficient data from the use of vinorelbine in pregnant women. Animal studies have shown vinorelbine was embryotoxicity and teratogenicity (see section 5.3). On the basis of the results of animal studies and the pharmacological action of the medicinal product, there is a potential risk of embryonic and foetal abnormalities.

There for, vinorelbine should not be used during pregnancy, unless the individually expected benefits clearly outweigh the possible risks.

If pregnancy occurs during treatment the patient should be informed about the risks for the unborn child and be monitored carefully. The possibility of genetic counselling should be also considered.

Contraception for men and women

Due to the genotoxic potential of vinorelbine (see section 5.3), women of child-bearing potential should use effective methods of contraception during treatment with vinorelbine and for 7 months after the end of therapy.

Men should use effective contraception during treatment and for 4 months after the end of therapy.

Vinorelbine is genotoxic, so genetic counselling is also recommended if the patient wishes to have children after treatment.

Breastfeeding

It is not known whether vinorelbine is excreted in human milk. The passage of vinorelbine into breast milk has not been studied in animal studies. Since a risk to the infant cannot be excluded, the infant must be weaned before starting treatment with Vinorelbin "Ebewe" (see section 4.3).

Fertility

Men being treated with vinorelbine are advised not to father children during treatment and for 4 months after the end of therapy. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with vinorelbine.

3.7 Effects on the ability to drive and use machines

3.8 **No studies of the effects on the ability to drive and use machines have been performed. In view of the undesirable effect profile of vinorelbine, it is recommended that appropriate caution be exercised when driving and operating machines during treatment with this substance. Adverse reactions**

The undesirable effects observed are listed below according to system organ classes and frequency with the MedDRA convention.

The following categories are used to define the frequency of undesirable effects:

Very common ($\geq 1/10$)

common ($\geq 1/100$, $< 1/10$)
uncommon ($\geq 1/1,000$, $< 1/100$)
rare ($\geq 1/10,000$, $< 1/1,000$)
very rare ($< 1/10,000$)
not known (cannot be estimated from the available data).

The most frequently reported adverse drug reactions are bone marrow depression with neutropenia, anaemia, neurologic disorders, gastrointestinal toxicity with nausea, vomiting, stomatitis and constipation, temporary increases in liver enzymes, alopecia and local phlebitis.

Other undesirable effects, summarised from post-authorisation reports and clinical studies have been added according to the MedDRA classification and with the frequency “*not known*”.

Detailed information on the undesirable effects:

The undesirable effects are categorized according the WHO classification (grade 1 = G1; grade 2 = G2; grade 3 = G3; grade 4 = G4; grade 1–4 = G1–4; grade 1–2 = G1–2; grade 3–4 = G3–4).

Infections and infestations

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|------------|--|
| Common: | - Viral, bacterial, or fungal infections at different localization (respiratory, urinary, GI tract) in mild to moderate severity and usually reversible with appropriate treatment |
| Uncommon: | - Severe sepsis sometimes with other organ failure
- Septicaemia |
| Very rare: | - Complicated septicaemia with a potentially fatal course |
| Not known: | - Neutropenic sepsis
- Neutropenic infection G3-4 |

Blood and lymphatic system disorders

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|--------------|---|
| Very common: | - Bone marrow depression resulting mainly in neutropenia (G3: 24.3%; G4: 27.8% with monotherapy), reversible within 5 - 7 days and non-cumulative |
| | - Anaemia (G3-4: 7.4% with monotherapy) |
| Common: | - Thrombocytopenia (G3-4: 2.5%) can occur, but is rarely severe |
| Not known: | - Febrile neutropenia
- Pancytopenia
- Leucopenia G1-4 |

Immune system disorders

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|---------|---|
| Common: | -Allergic reactions (skin reactions, respiratory reactions) |
| Rare: | - Systemic allergic reactions as anaphylactic shock, anaphylaxis, angio-oedema or anaphylactoid reactions |

Endocrine disorders

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|------------|--|
| Very Rare: | - Syndrome of inappropriate antidiuretic hormone secretion (SIADH) |
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Metabolism and nutrition disorders

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|-------|------------------------|
| Rare: | - Severe hyponatraemia |
|-------|------------------------|

Not known: - Anorexia

Nervous system disorders

Very common: -Neurologic disorders (G 3-4: 2.7%) including loss of deep tendon reflexes. Weakness of the lower extremities after prolonged use
Common: -Severe paraesthesia with sensory and motor symptoms, which are usually reversible
Uncommon: -Paralytic ileus (see also “Gastrointestinal disorders”)
Very rare: -Guillain-Barré syndrome
Not known: -Headache, dizziness, ataxia, posterior reversible encephalopathy syndrome

Cardiac disorders

Uncommon: - Cardiac ischemia (angina pectoris, myocardial infarction sometimes fatal) tachycardia, cardiac arrhythmia
Rare: - Reversible changes in electrocardiogram, palpitations
Not known: - Heart failure

Vascular disorders

Uncommon: - Arterial hypotension, arterial hypertension, flushing and peripheral coldness
Rare: - Severe hypotension, collapse
Not known: - Pulmonary embolism

Respiratory, thoracic and mediastinal disorders

Uncommon: - Dyspnoea and bronchospasm (as with other vinca alkaloids)
Rare: - Interstitial lung disease, sometimes fatal
Not known: -Respiratory insufficiency with fatal outcome after previous radiotherapy
- Cough G1-2
- Acute respiratory distress syndrome, sometimes fatal

Gastrointestinal disorders

Very common: - Oesophagitis, Stomatitis (G1-4: 15% with monotherapy),
- Nausea, vomiting (G1-2: 30.4% and G3-4: 2.2% with monotherapy); Constipation (G3-4: 2.7% with monotherapy, G3-4: 4.1% when combined with other chemotherapeutic agents), which occasionally develops into paralytic ileus.
Common: - Diarrhoea, usually mild to moderate
Uncommon: - Paralytic ileus (see also “Nervous system disorders”),
Rare: - Pancreatitis
Not known: - Gastrointestinal haemorrhages, abdominal pain

Hepatobiliary disorders

- Very common: - Temporary increase in liver enzymes (G1-2) without clinical symptoms (SGOT: 27.6%; SGPT: 29.3%)
- Not known: - Hepatic dysfunction

Skin and subcutaneous tissue disorders

- Very common: - Alopecia usually mild (G3-4: 4.1% in monotherapy)
- Common: - Generalised skin reactions such as rash, pruritus, urticaria
- Not known: - Palmoplantar erythrodysesthesia syndrome, skin hyperpigmentation (supravenous, serpiginous hyperpigmentation)

Musculoskeletal and connective tissue disorders

- Common: - Myalgia, arthralgia (including jaw pain)

Renal and urinary disorders

- Common: - Increase in creatinine
- Not known: - Renal failure

General disorders and administration site conditions

- Very common: - Vein irritation, reactions at the injection site such as erythema, burning pain, discolouration of the vein, local phlebitis (G 3-4: 3.7% under monotherapy)
- Common: - Asthenia, fatigue, fever, pain in different locations including chest pain and tumour pain
- Rare: - Local necrosis (injection site necrosis)
- Not known: - Chills G1-2

Examinations :

- Not known: - Weight loss

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form via the following link:

<https://sideeffects.health.gov.il>

3.9 Overdose

Overdosage can cause severe bone marrow depression with fever and infections. Paralytic ileus has also been reported.

As there is no specific antidote for an overdose with vinorelbine, symptomatic measures are necessary in the event of an overdose. These measures include:

- continuous monitoring of vital signs and particularly careful monitoring of the patient

- daily blood count in order to recognise the need for transfusions, for the administration of growth factors or for intensive medical care in good time, and to be able to assess the risk of infection
- measures to prevent paralytic ileus
- monitoring of the circulatory system and liver function.

Infection-related complications can be treated with broad-spectrum antibiotics; paralytic ileus, with decompression via a tube.

4. PHARMACOLOGICAL PROPERTIES

4.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vinca alkaloids and analogues - ATC code: L01 C A04

Vinorelbine bis[(R,R)-tartrate], or vinorelbine, is an antineoplastic substance from the group of vinca alkaloids. Vinorelbine, the active substance of Vinorelbin "Ebewe", differs from the other members of this substance group in that the catharanthine portion of the molecule is structurally modified.

Vinorelbine acts on the tubulin microtubule system of the cell. It prevents the polymerisation of tubulin, attaching preferentially to mitotic microtubules. Axonal microtubules are only affected at high concentrations of the active substance. The induction of tubulin spiralization is less than that produced by vincristine. Vinorelbine blocks mitosis in the G2 and M phase, causing cell death in interphase or at the following mitosis phase.

Paediatric population

The safety and efficacy of vinorelbine in paediatric patients have not been established. Clinical data from two single arm Phase II studies using intravenous vinorelbine in 33 and 46 paediatric patients with recurrent solid tumours, including rhabdomyosarcoma, other soft tissue sarcoma, Ewing sarcoma, liposarcoma, synovial sarcoma, fibrosarcoma, central nervous system cancer, osteosarcoma, neuroblastoma, showed no meaningful clinical activity. Intravenous doses of 30 to 33.75 mg/m² BSA were used, administered either on day 1 and day 8 in a 3 week cycle or once a week for 6 weeks in an 8 week cycle. The toxicity profile was comparable to that reported in adult patients (see section 4.2).

4.2 Pharmacokinetic properties

The pharmacokinetic parameters were determined in the blood.

Distribution

The volume of distribution at steady state is high on average at 21.2 l/kg, ranging between 7.5–39.7 l/kg, and indicates a considerable tissue distribution.

Binding to plasma proteins is weak (13.5%). However, vinorelbine binds strongly to blood cells, especially thrombocytes (78%).

Vinorelbine accumulates in the lung tissue. An investigation of biopsy material showed the concentration in lung tissue to be 300 times higher than in serum. Vinorelbine is not found in the central nervous system.

It has been shown that intravenously administered vinorelbine exhibits linear pharmacokinetics up to doses of 45 mg/m² BSA.

Biotransformation

With the exception of 4-O-deacetylvinorelbine, which is probably formed by carboxylesterases, the metabolites of vinorelbine are formed via CYP3A4, an isoform of cytochrome P450. All metabolites were identified and are all inactive, except 4-O-deacetylvinorelbine, the main metabolite in the blood. Glucuronidation and sulphation are not involved in the metabolism of vinorelbine.

Elimination

After intravenous bolus injection or infusion in humans, vinorelbine is tri-exponentially eliminated from the blood. This is followed by a slow elimination phase with a long terminal half-life.

The mean terminal half-life is about 40 hours on average. Blood clearance is high, almost reaching the value for hepatic circulation, and averages 0.72 l/h/kg, ranging between 0.32–1.26 l/h/kg.

Renal elimination of unchanged vinorelbine is low (<20% of the dose). Biliary excretion is the predominant route of elimination both for metabolites and for unchanged vinorelbine (the main recovered compound).

Special populations

Renal and hepatic impairment

In patients with liver metastases, changes in mean vinorelbine clearance only occurred when more than 75% of the liver was affected.

An initial study reported on the effects of hepatic dysfunction on the pharmacokinetics of vinorelbine. This study was conducted in breast cancer patients with liver metastases and showed that a change in the average clearance of vinorelbine only occurred when the liver was involved by more than 75%. A dose-adjusted phase I pharmacokinetic study was conducted in cancer patients with hepatic dysfunction: Six patients with moderate hepatic dysfunction (bilirubin $\leq 2 \times$ UNL and transaminases $\leq 5 \times$ UNL) were treated with up to 25 mg/m² BSA, and eight patients with severe hepatic dysfunction (bilirubin $> 2 \times$ UNL and/or transaminases $> 5 \times$ UNL) received up to 20 mg/m² BSA. In these two patient subgroups, the mean total clearance corresponded to that of patients with normal liver function. It can therefore be concluded that the pharmacokinetics of vinorelbine are not impaired in patients with moderate to severe liver dysfunction.

Nevertheless, in the case of severe liver dysfunction, a reduced dose of 20 mg/m² BSA and close monitoring of haematological parameters is recommended as a precautionary measure (see sections 4.2 and 4.4).

The effects of renal dysfunction on the pharmacokinetics of vinorelbine have not been investigated. However, due to the low renal excretion, there is no need to reduce the dose in the event of renal insufficiency.

Elderly patients

A study of Vinorelbine "Ebewe" in elderly patients (≥ 70 years) with non-small cell lung cancer showed no influence of age on the pharmacokinetics of vinorelbine. However, due to the

generally higher sensitivity in older patients, caution is advised when increasing the dose of Vinorelbine "Ebewe" (see section 4.2).

Pharmacokinetic/pharmacodynamic relationship

A close correlation has been demonstrated between the concentration in the blood and the reduction of leukocytes and neutrophils.

Pharmacokinetic/pharmacodynamic relationships

A strong relationship has been demonstrated between vinorelbine blood exposure and of leucocytes or polynuclear neutrophil decreases.

4.3 Preclinical safety data

Acute and chronic toxicity

Signs of overdose in test animals included hair loss, behavioural abnormalities (exhaustion, drowsiness), lung damage, weight loss and more or less pronounced bone marrow hypoplasia. In acute and chronic toxicity studies, dose-dependent myelotoxicity was observed in several animal species, affecting all bone marrow cells. Occasionally, there was also atrophy of the lymphatic and splenic follicles. In animal trials, high doses led to an increase in liver enzymes as a sign of hepatotoxicity.

Mutagenic and carcinogenic potential

Vinorelbine induces chromosomal damage, but shows no mutagenic potential in the Ames test. In animal studies vinorelbine induced aneuploidy and polyploidy. It can be assumed that vinorelbine can also cause genotoxic effects in humans (aneuploidy and polyploidy). The results for carcinogenic potential in the mouse and rat were negative but only low doses have been tested.

Reproductive toxicity studiesology

In animal reproductive studies, effects were observed at subtherapeutic dosages. Embryo- and foetotoxicity were seen, such as intra-uterine growth retardation and delayed ossification. Teratogenicity (fusion of the vertebrae, missing ribs) was observed at maternal toxic doses. In addition, spermatogenesis and secretion of prostate and seminal vesicles were reduced, but fertility in rats was not diminished.

Safety pharmacology

Safety pharmacology studies performed in the dog and in the monkey did not reveal any adverse effect on the cardio-vascular system.

5. PHARMACEUTICAL PARTICULARS

5.1 List of excipients

Water for injections.

5.2 Incompatibilities

Vinorelbine "Ebewe" should not be diluted in alkaline solutions (risk of precipitation). This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

5.3 Shelf life

Unopened package: The expiry date of the product is indicated on the packaging materials.
Opened sales package: an opened sales package should be used immediately and any unused remaining solution should be disposed of.

Diluted preparation:

The stability of infusion solutions prepared from Vinorelbine "Ebewe" concentrate for solution for infusion with appropriate infusion vehicles (5% glucose, 0.9% sodium chloride) has been shown at concentrations of 0.5 mg/ml and 3.0 mg/ml. Infusion solutions remain stable for 28 days when stored in a refrigerator or at room temperature with protection from light.

If the solution is stored at room temperature without protection from light, it is stable for 4 days.

From a microbiological point of view, the 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.

5.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Keep the vial in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

5.5 Nature and contents of container

Vinorelbine "Ebewe" is available in colourless type I glass vial, with fluoropolymer-coated rubber stopper, sealed with aluminium crimp caps.

Vials with 1 ml (10 mg of vinorelbine) and 5 ml (50 mg of vinorelbine).

Pack size: 1 vial.

5.6 Special precautions for disposal and other handling

The preparation of injection or infusion solutions of cytotoxic medicinal products must be carried out by specially trained personnel with knowledge of the medicinal products used, under conditions that ensure protection of the environment and in particular protection of the personnel involved. This requires that a workstation intended for this purpose is made available. It is forbidden to smoke, eat or drink in this area

Personnel must be provided with suitable working materials, in particular long-sleeve gowns, protective masks, headgear, safety glasses, sterile disposable gloves, protective covers for the workplace, containers and waste collection bins.

Syringes and infusion sets must be stored carefully to prevent leakage.

Spills and leakages must be wiped up.

Precautions must be taken to avoid exposure to personnel who are pregnant.

All Any eye contact with the eye must be strictly avoided. After eye contact, rinse immediately with physiological sodium chloride solution. In the event of irritation, consult an ophthalmologist. In case of skin contact, rinse thoroughly with water immediately.

After completion, any exposed surface should be thoroughly cleaned and hands and face washed.

There is no incompatibility between Vinorelbin "Ebewe" and clear glass vials, PVC or infusion sets with PVC tubing.

Vinorelbin "Ebewe" may be administered by slow bolus (6-10 minutes) after dilution in 20-50 ml of normal saline or glucose 50 mg/ml (5%) solution or by a short infusion (20-30 minutes) after dilution in 125 ml of normal saline or glucose 50 mg/ml (5%) solution. Administration should always be followed by a normal saline infusion of at least 250ml to flush the vein.

Vinorelbin "Ebewe" should only be given intravenously. It is very important to make sure that the cannula is accurately placed in the vein before the injection is commenced. If Vinorelbin "Ebewe" infiltrates the surrounding tissue during intravenous administration, a substantial irritation may occur. In this case, the injection should be stopped, the vein flushed with saline solution and the rest of the dose should be administered in another vein. In the event of extravasation, glucocorticoids could be given intravenously to reduce the risk of phlebitis.

Excreta and vomit must be handled with care.

Any unused product or waste material should be disposed of in accordance with local requirements.

6. LICENSE HOLDER AND IMPORTER'S NAME AND ADDRESS

Sandoz Pharmaceuticals Israel Ltd., P.O.Box 9015, Tel Aviv, Israel

7. MARKETING AUTHORISATION NUMBER

136-44-31351-00

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