1. NAME OF THE MEDICINAL PRODUCT

Vinorelbin "Ebewe" 10 mg/ml

2. 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.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Vinorelbin "Ebewe" 10 mg/ml is a clear colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 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.

4.2 Posology and method of administration

Strictly intravenous administration after appropriate dilution.

Intra-thecal 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/m^2 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/m^2 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**).

4.3 Contraindications

- Hypersensitivity to vinorelbine or other vinca alkaloids, or to any of the excipients listed in section 6.1
- Neutrophil count < 1500/mm^3 or severe infection currently or recently (within 2 weeks)
- Platelet count < 100,000/mm^3
- In combination with yellow fever vaccine (see section 4.5)
- Breast-feeding (see section 4.6)

4.4 Special warnings and precautions for use

Special warnings

Vinorelbin "Ebewe" should be administered under the supervision of a physician experienced

in the use of chemotherapy.
Strictly for intravenous use only.

Close haematological monitoring should be performed during treatment (determination of haemoglobin level and number of leucocytes, neutrophils and platelets before each new infusion), since inhibition of the haematopoietic system is the main risk during treatment with vinorelbine.

The dose has to be determined according to the haematological status.

- Neutropenia, which is non-cumulative and has its nadir between day 7 and 14 after administration, and is quickly reversible within 5-7 days, is the main dose-limiting adverse reaction. If the number of neutrophil granulocytes is below 1500/mm^3 and/or the platelet count is below 100000/mm^3, the treatment should be postponed until recovery.

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

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

Special precautions for use

- Special caution is advised in patients with a history of ischaemic heart disease (see section 4.8).
- The pharmacokinetics of vinorelbine is not modified in patients presenting moderate or severe liver impairment. For dosage adjustment in this specific patient group, 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.
- Vinorelbin "Ebewe" 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, immediately rinse the eye with normal saline solution and contact an ophthalmologist.
- Strong inhibitors or inducers of CYP3A4 can affect the vinorelbine concentration and caution should therefore be exercised (see section 4.5 Interactions specific to vinorelbine), and its combination with phenytoin (like all cytotoxics) and with itraconazole (like all vinca alkaloids) is not recommended.
- This product is generally not recommended in combination with live attenuated vaccines and is specifically contra-indicated with yellow fever vaccine.
- Women of child-bearing potential must use effective contraception during treatment and up to 7 months after treatment (see section 4.6). For information on pregnancy, breast feeding and fertility, please refer to section 4.6.

4.5 Interactions with other medicinal products and other forms of interactions

Interactions common to all cytotoxics:

Due to the increased risk of thrombosis in cancer patients, the use of anticoagulant therapy is frequent. The high individual variability of coagulation in cancer patients, together with the possibility of interaction between oral anticoagulants and chemotherapy, should lead to an increase in the frequency of INR (International Normalised Ratio) monitoring in case of

treatment with oral anticoagulants.

Concomitant uses contraindicated:

Yellow fever vaccine: risk of fatal generalised vaccine disease (see section 4.3).

Concomitant uses not recommended:

Live attenuated vaccines (for yellow fever vaccine, see contraindicated concomitant use):
Risk of generalised vaccine disease, possibly fatal.
This risk is increased in patients already immunosuppressed by their underlying disease.
It is recommended to use an inactivated vaccine if there is one (e.g. poliomyelitis) (see section 4.4).

With concomitant administration of phenytoin there is the risk of exacerbation of convulsions resulting from a decreased phenytoin absorption as well as the risk of decreased efficacy of the cytostatic due to increased hepatic metabolism induced by phenytoin. This combination is not recommended.

Concomitant uses to take into consideration:

Cyclosporine, tacrolimus: Excessive immunosuppression with risk of lymphoproliferation.

Specific interactions with vinca alkaloids:

Concomitant use not recommended:

Itraconazole: Increased neurotoxicity of vinca alkaloids due to a decrease in the hepatic metabolism.

Concomitant use to take into consideration:

Mitomycin C: Risks of bronchospasm and dyspnoea are increased. In rare cases, an interstitial lung disease was observed.

As vinca alkaloids are known substrates for P-glycoprotein, and in the absence of specific studies, caution should be exercised when combining vinorelbine with strong modulators of this membrane transporter.

Vinorelbine-specific interactions:

The combination of vinorelbine with other drugs with known bone marrow toxicity is likely to exacerbate the myelosuppressive adverse effects.

CYP3A4 is the main enzyme involved in the metabolism of vinorelbine, and the combination with a drug that induces (such as phenytoin, phenobarbital, rifampicin, carbamazepine,

Hypericum perforatum) or inhibits (such as itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin, nefazodone), this iso-enzyme can decrease or increase the concentration of vinorelbine in the blood.

The combination vinorelbine-cisplatin (a very common combination) shows no interaction with respect to the pharmacological parameters of vinorelbine over several cycles of treatment. However, a higher incidence of granulocytopenia has been reported in patients receiving combination therapy with vinorelbine and cisplatin than in those receiving vinorelbine alone.

An increased incidence of grade 3/4 neutropenia has been suggested when vinorelbine IV and lapatinib were combined in a phase I clinical trial. In this trial, the recommended dose of vinorelbine IV in a three-week regimen on days 1 and 8 was 22.5 mg/m^2 in combination with a daily dose of lapatinib 1000 mg. This type of combination should be administered with caution.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are insufficient data from the use of vinorelbine in pregnant women. In animal reproductive studies vinorelbine was embryotoxicand feto-lethal and teratogenic (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.
During pregnancy this product should not be used, unless the individual awaited benefit clearly outweighs the potential 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.

Women of child-bearing age
Women of child-bearing potential must use effective methods of contraception during and up to 7 months after treatment with Vinorelbin "Ebewe" and should inform their doctor if they become pregnant.

Breastfeeding
It is unknown whether vinorelbine is excreted in human breast milk. The excretion of vinorelbine in milk has not been studied in animal studies. A risk to the child cannot be excluded. Consequently, breastfeeding must be discontinued before starting treatment with Vinorelbin "Ebewe" (see section 4.3).

Fertility
Vinorelbine can have genotoxic effects. Therefore, men being treated with vinorelbine are advised not to father a child during and for minimum of 4 months following cessation of treatment. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with vinorelbine.

4.7 Effects on the ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed; however, based on its pharmacodynamic profile, vinorelbine is unlikely to impair the ability to drive or operate machinery.

However, caution is necessary in patients treated with vinorelbine considering some adverse reactions of the drug.

4.8 Adverse reactions

Adverse reactions reported as more than isolated cases are listed below: ranked by system organ and by frequency.
Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), very rare (< 1/10,000), according to the MedDRA frequency convention and system organ classification.

The most commonly reported adverse reactions are: bone marrow depression with neutropenia, anaemia, neurologic disorders, gastrointestinal toxicity with nausea, vomiting, stomatitis and constipation, transient elevations of liver function tests, alopecia and local phlebitis.

Additional adverse reactions pooled from post marketing experience and clinical trials have been added according to the MedDRA classification with the frequency "*Not known*".

Detailed information:

Reactions were described using 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

Common:	- Bacterial, viral or fungal infection in various locations (respiratory, gastrointestinal, urinary) of mild to moderate intensity and generally reversible with an appropriate treatment
Uncommon:	- Severe sepsis sometimes with other organ failure - Septicaemia
Very rare:	- Complicated septicaemia, sometimes fatal
Not known:	- Neutropenic sepsis - Neutropenic infection G3-4

Blood and lymphatic system disorders

Very common:	- Bone marrow depression resulting mainly in neutropenia (G3: 24.3%; G4: 27.8%), reversible within 5 to 7 days and non-cumulative over time - Anaemia (G3-4: 7.4%)
Common:	- Thrombocytopenia (G3-4: 2.5%) may occur but is seldom severe
Not known:	- Febrile neutropenia - Pancytopenia

- Leucopenia G1-4

Immune system disorders

Common: -Allergic reactions (skin reactions, respiratory reactions).

Not known: - Systemic allergic reactions, such as anaphylactic shock, anaphylaxis, or anaphylactoid reactions

Endocrine disorders

Not known: - Inappropriate antidiuretic hormone secretion (SIADH)

Metabolism and nutrition disorders

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 treatment with long duration.
Uncommon: -Severe paraesthesia with sensory and motor symptoms (G3-4: < 3%). These effects are generally reversible when the treatment is discontinued.
Rare: -Effects on the autonomic nervous system causing intestinal paresis and constipation. Seldom this progresses to paralytic ileus (see also "Gastrointestinal disorders")
Very rare: -Guillain-Barré syndrome
Not known: -Headache, dizziness, ataxia, posterior reversible encephalopathy syndrome

Cardiac disorders

Rare: - Ischemic heart disease (angina pectoris, myocardial infarction, sometimes fatal)
Very rare: - Tachycardia, palpitation and heart rhythm disorders

Not known: - Heart failure

Vascular disorders

Uncommon: - Arterial hypotension, arterial hypertension, flushing and peripheral coldness
Rare: - Severe hypotension, collapse

Respiratory, thoracic and mediastinal disorders

Uncommon: - Dyspnoea and bronchospasm may occur in association with vinorelbine as with other vinca alkaloids
Rare: - Interstitial lung disease, sometimes fatal, has been reported
Not known: - Cough G1-2

Gastro-intestinal disorders

Very common:	- Stomatitis (G1-4: 15% with vinorelbine in monotherapy) - Nausea and vomiting (G1-2: 30.4% and G3-4: 2.2%). Anti-emetic therapy may reduce their occurrence - Constipation is the main symptom (G3-4: 2.7%) which rarely progresses to paralytic ileus with vinorelbine in monotherapy and (G3-4: 4.1%) with the combination of vinorelbine and other chemotherapeutic agents
Common:	- Usually mild to moderate diarrhoea may occur
Rare:	- Paralytic ileus, treatment may be resumed after recovery of normal bowel mobility - Pancreatitis has been reported
Not known:	- Gastrointestinal bleeding - Severe diarrhoea - Abdominal pain

Hepatobiliary disorders

Very common:	-Abnormal liver function values (total bilirubin increased, alkaline phosphatase increased, aspartate aminotransferase increased, alanine aminotransferase increased) (G 1-2) without clinical symptoms were reported (bilirubin, alkaline phosphatase, ASAT in 27,6% and ALAT in 29,3%)
Not known:	-Impaired hepatic function

Skin and subcutaneous tissue disorders

Very common:	- Usually mild alopecia may occur (G3-4: 4.1% with vinorelbine in monotherapy)
Rare:	- Generalised cutaneous reactions have been reported with vinorelbine
Not known:	- Palmar-plantar erythrodysesthesia syndrome, skin hyperpigmentation (serpentine supravenous hyperpigmentation)

Musculoskeletal and connective tissue disorders

Common:	- Arthralgia including jaw pain and myalgia

General disorders and administration site conditions

Very common:	- Reactions at the injection site may include erythema, burning pain, vein discolouration and local phlebitis (G3-4: 3.7% with vinorelbine in monotherapy)
Common:	- Asthenia, fatigue, fever, pain in different locations, including chest pain and pain at the tumour site have been experienced by patients receiving vinorelbine

Rare:	- Local necrosis has been observed. Proper positioning of the intravenous needle or catheter and bolus injection followed by liberal flushing of the vein can limit these effects
Not known:	- Chills G1-2

Investigations:

Not known:	- Weight loss

For the oral formulation of vinorelbine the following additional adverse reactions were reported: taste disorder, visual impairment, insomnia, dysphagia, oesophagitis, neuromotor disorders, weight gain, dysuria, other genitourinary symptoms.

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

4.9 Overdose

Symptoms:
Overdosing with vinorelbine could produce bone marrow hypoplasia sometimes associated with infection, fever and paralytic ileus.

Treatment :
General support measures together with blood transfusion, growth factors administration and broad spectrum antibiotic therapy should be instituted as deemed necessary by the physician.

Antidote:
There is no known antidote for a vinorelbine overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Vinorelbine is an antineoplastic drug of the vinca alkaloid family but unlike all the other vinca alkaloids, the catharanthine moiety of vinorelbine has been structurally modified. At molecular level, it acts on the dynamic equilibrium of tubulin in the microtubular apparatus of the cell. It inhibits tubulin polymerization and binds preferentially to mitotic microtubules, affecting axonal microtubules at high concentrations only. The strength of tubulin spiralization is less than that produced by vincristine.

Vinorelbine blocks mitosis in G2-M, causing cell death in interphase or in the following mitosis.

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 at doses of 30 to 33.75 mg/m² D1 and D8 every 3 weeks or once a week for 6 weeks every 8 weeks, showed no meaningful clinical activity. The toxicity profile was similar to that reported in adult patients (see section 4.2).

5.2 Pharmacokinetic properties

The pharmacokinetic parameters were assessed in the blood.

Distribution
The steady-state volume of distribution is large: 21.2 l/kg (range: 7.5-39.7 l/kg) indicating extensive tissue distribution.
Binding to plasma protein is low (13.5%). However, vinorelbine binds strongly to blood cells and especially to platelets (78%).
There is significant uptake of vinorelbine in the lungs, as assessed by surgical lung biopsies, which showed concentrations up to 300 times higher than in serum. Vinorelbine was not found in the central nervous system.

Biotransformation
All metabolites of vinorelbine are formed by the CYP3A4 isoform of cytochromes P450, except 4-O-deacetylvinorelbine, which seems to be formed by carboxylesterases. 4-O-deacetylvinorelbine is the only active metabolite and the main one observed in the blood. Neither sulphate nor glucuronide conjugates were found.

Elimination
The mean terminal half-life of vinorelbine is around 40 hours. Blood clearance is high, approaching hepatic blood flow, and is 0.72 $l.h^{-1}.kg^{-1}$ on average (range: 0.32 – 1.26 $l.h^{-1}.kg^{-1}$).
Renal elimination is low (< 20% of the intravenous dose administered) and consists mostly of parent compound. Biliary excretion is the principal elimination route for both metabolites and unchanged vinorelbine (the main compound recovered).

<u>Special populations</u>

Renal and liver function failure

The effects of renal impairment on the pharmacokinetics of vinorelbine have not been studied. However, dose reduction in case of impaired renal function is not indicated due to the low renal elimination.

A first study has reported the effects of liver impairment on vinorelbine pharmacokinetics. This study was performed in patients with liver metastases due to breast cancer, and concluded that a change in the mean clearance of vinorelbine was only observed when more

than 75% of the liver is involved. A phase I pharmacokinetic dose-adjusted study was conducted in cancer patients with liver dysfunction: 6 patients with moderate impairment (bilirubin < 2 x UNL and transaminases < 5 x UNL) treated with the highest dose of 25 mg/m^2 and 8 patients with severe impairment (bilirubin > 2 x UNL and/or transaminases > 5 x UNL) treated with a dose of 20 mg/m². Mean total clearance in these patients was similar to that in patients with normal hepatic function. Consequently, the pharmacokinetics of vinorelbine is not modified in patients with moderate or severe liver impairment. Nevertheless, as a precautionary measure, a reduced posology of 20 mg/m² and close monitoring of haematological parameters is recommended in patients with severe liver impairment (see sections 4.2 and 4.4).

Elderly patients

A study with vinorelbine in elderly patients (≥ 70 years) with NSCLC demonstrated that the pharmacokinetics of vinorelbine was not influenced by age. However, since elderly patients are frail, caution should be exercised when increasing the dose of vinorelbine (see section 4.2 – Posology and method of administration).

Pharmacokinetic/pharmacodynamic relationships

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

5.3 Preclinical safety data

Vinorelbine induced chromosome changes but was not mutagenic in the Ames test.
It is assumed that vinorelbine can cause mutagenic effects (induction of aneuploidy of polyploidy) in man.
In animal reproductive studies, vinorelbine was embryo-foeto-lethal and teratogenic.
No haemodynamic effects were found in dogs receiving vinorelbine at maximal tolerated dose; only some minor, non-significant disturbances of repolarisation were observed as with other vinca alkaloids tested. No effect on the cardiovascular system was observed in primates receiving repeated doses of vinorelbine over 39 weeks.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections.

6.2 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.

6.3 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.

6.4 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.

6.5 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.

6.6 Special precautions for disposal and other handling

Only trained staff should carry out the preparation and administration of Vinorelbin "Ebewe". Suitable safety equipment, disposable gloves, facemask and disposable apron should be worn. Spills and leakages must be wiped up.
All contact with the eye must be strictly avoided. If this occurs, immediately rinse the eye with normal saline solution and contact an ophthalmologist.

On 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 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.

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

7. LICENSE HOLDER AND IMPORTER'S NAME AND ADDRESS

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

8. MARKETING AUTHORISATION NUMBER

136-44-31351-00

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