1. **NAME OF THE MEDICINAL PRODUCT**

Eberelbin

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

1ml contains 13.85mg vinorelbine tartrate equivalent to 10mg/ml vinorelbine base as active ingredient.
For excipients, see 6.1.

3. **PHARMACEUTICAL FORM**

Concentrate for solution for infusion.
Clear, colourless to pale yellow solution.
The diluted solution for infusion is a clear, colourless or pale yellow solution.

4. **Clinical particulars**

4.1 Therapeutic indications

- Non-small cell lung cancer
- Advanced breast cancer

4.2 Posology and method of administration

Only for intravenous administration. The use of the intrathecal route is strictly contraindicated.
Vinorelbine concentrate for solution for infusion must be administered intravenously only. Before application it is extremely important to ensure that the intravenous needle is positioned in the vein. Leakage into surrounding tissue during administration of vinorelbine may cause considerable irritation. If extravasation occurs, the injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein.

Adults:

As monotherapy the usual dose is 25–30mg/m² weekly.
In combination therapy the same dose may be administered, but the number of applications are reduced so that 25–30mg/m² is given e.g. every third week days 1 and 5 or every third week days 1 and 8.
Vinorelbine may be administered by slow bolus (5–10 minutes) after dilution in 20–50ml of normal saline solution or by a short infusion (20–30 minutes) after dilution in 125ml of normal saline solution. Administration should always be followed by a normal saline infusion to flush the vein.

Dose adjustment

- In patients with severe hepatic dysfunction; the dose of vinorelbine should be reduced.
- In patients with renal insufficiency a dose reduction is not needed as vinorelbine is predominantly excreted by the biliary route.
- During therapy the hematologic condition of the patient should be carefully monitored.

Max. single-dose is: about 35mg/m²
Max. dose per treatment is: 60mg

4.3 Contraindications

Hypersensitivity to the active substance.
Severe hepatic insufficiency, not related to the tumoral process.
Pregnancy.
Lactation.

4.4 Special warnings and special precautions for use

- Vinorelbine concentrate for solution for infusion must only be administered by the intravenous route. The use of intrathecal route is contraindicated.
- Treatment should be undertaken with close haematological monitoring (determination of haemoglobin level and number of leucocytes, granulocytes and platelets before each new injection); if the neutrophil count is <2000/mm³, treatment should be delayed until recovery and the patient should be observed.
- If the patient presents signs or symptoms suggestive of infection, a prompt investigation should be carried out.
- If there is significant hepatic impairment the dose should be reduced.
- In case of renal impairment, because of the low level of renal excretion, no dose modification is necessary.
- Vinorelbine should not be given concomitantly with radiotherapy if the treatment field includes the liver.
- All contact with the eye should be strictly avoided: risk of severe irritation and even corneal ulceration if the drug is sprayed under pressure. Immediate liberal washing of the eye with normal saline solution should be undertaken if any contact occurs.

4.5 Interaction with other medicinal products and other forms of interaction

The pharmacokinetics are not influenced by concurrent administration of cisplatin with vinorelbine concentrate for solution for infusion.

4.6 Pregnancy and lactation

In animal reproductive studies vinorelbine was embryo- and feto-lethal and teratogenic.
Women should not become pregnant during treatment with vinorelbine.
This product should not be used during pregnancy.
If pregnancy should occur during treatment, the possiblility of genetic counselling should be used.
It is not known whether vinorelbine passes into the breast milk. Lactation must therefore be discontinued before treatment wiht this medicine.

4.7 Effects on ability to drive and use machines

Unknown.

4.8 Undesirable effects

- **Blood and the lymphatic system disorders**
  - The limiting toxicity is neutropenia (G1: 9.7%; G2: 15.2%; G3: 24.3%; G4: 27.8%) which is rapidly reversible (5 to 7 days) and non-cumulative; it is maximal between 5 and 7 days after administration. Further treatment may be given after recovery of the granulocyte count.
  - Anaemia (G1–2: 61.2%; G3–4: 7.4%) and thrombocytopenia (G1–2: 5.1%; G3–4: 2.5%) are seldom severe.
- **Immune system disorders**
  - Like other vinca alkaloids vinorelbine may cause dyspnea and bronchospasm rarely and very rarely local or generalised skin reactions.
- **Nervous system disorders**
  - Peripheral
    This is generally limited to loss of deep tendon reflexes; severe paraesthesiae are uncommon (G1: 17.2%; G2: 3.6%; G3: 2.6%; G4: 0.1%). The effects are dose dependent but reversible when treatment is discontinued.
  - Autonomic neuropathy
    The main symptom is intestinal paresis causing constipation (G1: 16.9%; G2: 4.9%) which rarely progresses to paralytic ileus (G3: 2%); G4: 0.7%).
    Treatment may be resumed after recovery of normal bowel mobility.
- **Vascular disorders**
  Burning pain at the injection site and local phlebitis (G1: 12.3%; G2: 8.2%; G3: 3.6%; G4: 0.1%) may occur with repeated injections of Eberelbin.
  Bolus injection followed by liberal flushing of the vein can limit this effect. Insertion of a central venous line may be necessary.
- **Gastrointestinal disorders**
  - Constipation (see autonomic neuropathy)
  - Diarrhoea (G1: 7.6%; G2: 3.6%; G3: 0.7%; G4: 0.1%) : severe diarrhoea is uncommon.
  - Nausea-vomiting (G1: 19.9%; G2: 8.3%; G3: 1.9%; G4: 0.3%) : severe nausea and vomiting may occasionally occur. Conventional anti-emetic therapy reduces these undesirable effects.
- **Skin and subcutaneous tissue disorders**
  - Alopecia is mild (G1–2: 21%) and may appear progressively with repeated courses of treatment (G3–4: 4.1%).

- **General disorders and administration site conditions**
  - Jaw pain has occasionally been reported.
  - Any extravasation may cause local reactions which rarely progress to necrosis (see 4.2. posology and method of administration).

4.9 Overdose

* Acute toxicity studies in animals

The symptoms of overdose are piloerection, behaviour abnormalities (lethargy, prostration), lung lesions, weight reduction with more or less severe bone marrow hypoplasia in animals sacrified during the course of the study.

* Symptoms of overdoses in humans may sometimes be fever, medullary aplasia, infection and a possible paralytic ileus. In the treatment of infectious complication broad-spectrum antibiotic therapy may be instituted and in the treatment of paralytic ileus, nasogastric aspiration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Plant Alkaloids, Vinca alkaloids and analogues,
ATC code: L01C A04

Vinorelbine concentrate for solution for infusion is a antineoplastic of the vinca alkaloid group.

The active substance vinorelbine has as its molecular target the dynamic balance of tubulin/ microtubule. Vinorelbine prevents the polymerisation of tubulin. The activity is targeted mainly on mitotic microtubules; axonal microtubules are affected at high concentration.

The vinorelbine spiralizing effect on tubulin is lower than that of vincristine. Vinorelbine inhibits the mitosis at phase G2-M and induces cell death at the interphase and at the following mitosis.

5.2 Pharmacokinetic properties

After intravenous administration, vinorelbine concentration in plasma is characterised by a triphasic elimination. The terminal phase half-life in plasma is over 40 hours.

Total clearance of vinorelbine is high (1.3l/h/kg) with excretion occurring mainly by the biliary route; renal excretion is low (18.5% of label is recovered in urine).

The active substance has a distribution volume of more than 40l/kg.

Vinorelbine has a moderate binding to plasma proteins (13.5%) and binding to thrombocytes is high (78%). Vinorelbine penetrates into lung tissue extremely well (from biopsy material the quotient for tissue/plasma-concentration was greater than 300).

Vinorelbine is eliminated primarily unchanged in the urine, only low deacetylvinorelbine concentrations have been recovered in humans.

5.3 Preclinical safety data

Mutagenic and carcinogenic potential

Vinorelbine is assumed to cause mutagenic effects because of its interaction with the spindle apparates during mitosis.

To avoid toxic effects in the carcinogenicty study vinorelbine was administered only once every two weeks and no carcinogenic potential was seen.

Reproductive toxicity

In animal studies vinorelbine was embryo- and feto-lethal and teratogenic.

Safety pharmacology

Bibliographic review concerning the tolerance of vinca alkaloids on the cardiovascular system shows the occurrence of some cardiac events (such as angina, myocardial infarction), but the incidence of these is low.

An ECG-study in dogs showed only some non significant repolarisation-disturbances. A 39-week-study on primates showed no cardiovascular effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections and nitrogen (inert filling).

6.2 Incompatibilities

Vinorelbine concentrate for solution for infusion must not be diluted with alkaline solutions due to the risk of precipitation. In case of polychemotherapy Eberelbin should not be mixed with other agents.

Vinorelbine concentrate for solution for infusion must not be mixed with other preparations except with those mentioned in 6.6.

Eberelbin is not absorbed to or affected by either PVC, PE or clear neutral glass.

6.3 Shelf life

Unopened package: 36 months

6.4 Special precautions for storage

Store at 2–8°C. Keep container in the outer carton.

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.

6.5 Nature and contents of container

Glas vials (type 1). The stopper is covered with a crimped-on aluminium cap equipped with a polypropylene flip-off cap.

1 vial containing 10mg/1ml
1 vial containing 50mg/5ml

6.6 Instructions for use and handling

Eberelbin 10mg/ml concentrate for solution for infusion may be diluted in either physiologic sodium chloride solution or 5% glucose solution for infusion. The quantity of diluent depends on the administration manner. Given as bolus injection the infusion concentrate is diluted in 20–50ml and when given as an infusion diluted in 125ml in one of the above mentioned diluents.

From a microbiological point of view, the product sould 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.

The maximum storage times for vinorelbine infusion solutions prepared in glucose 5% respectively sodium chloride 0.9% are 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.

The diluted solution for infusion is a clear, colourless or pale yellow solution.

Vinorelbine neither reacts with plastic nor with neutral colourless glass.

Handling guidelines: the preparation and administration of Eberelbin should be carried out only by trained staff and as with all cytotoxic agents, precautions should be taken to avoid exposing staff during pregnancy.

Preparation of solution for administration should be carried out in a designated handling area and working over a washable tray or disposable plastic-backed absorbent paper.

Care must be taken to avoid product contamination of the eye thereby causing severe irritation or even corneal ulcer. If exposure occurs, the eyes should immediately be thoroughly flushed with physiologic sodium chloride solution for 15 minutes.

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

7. MANUFACTURER

EBEWE Pharma Ges.m.b.H Nfg.KG
A-4866 Unterach, AUSTRIA

8. DATE OF (PARTIAL) REVISION OF THE TEXT

October 2003