Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vinorelbine 10 mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of concentrate for solution for infusion contains 10 mg of vinorelbine (as vinorelbine tartrate).

Each 1 ml concentrate for solution for infusion contains vinorelbine tartrate equivalent to 10 mg vinorelbine.
Each 5 ml concentrate for solution for infusion contains vinorelbine tartrate equivalent to 50 mg vinorelbine.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, colourless to pale yellow solution, and free from visible particles.
pH: 3 - 4

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Vinorelbine is indicated for the treatment of:
- Non small cell lung cancer (stage 3 or 4);
- As single agent in patients with metastatic breast cancer (stage 4), where treatment with anthracycline and taxane containing chemotherapy has failed or is not appropriate.

4.2 Posology and method of administration

For intravenous infusion only.

Vinorelbine 10 mg/ml concentrate for solution for infusion should be given in cooperation with a physician with extensive experience in therapy with cytostatics. The use of intrathecal route is contra-indicated.

For instructions regarding use and handling, see section 6.6.

Vinorelbine may be administered by slow bolus (5-10 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.

Non-small cell lung cancer: As a single agent the normal dose is 25-30 mg/m², administered once weekly.
In polychemotherapy the schedule regimen are a function of the protocol. The normal dose could be used (25-30 mg/m²), but the frequency of the administration be reduced to for example day 1 and 5 every third week or day 1 and 8 every third week according to the regimen.

Metastatic breast cancer: The normal dose is 25-30 mg/m², administered once weekly.
The maximum tolerated dose per administration: 35.4 mg/m^2 body surface area.
For patients with severely reduced hepatic function caution and careful monitoring of haematological parameters is recommended. The dose may have to be reduced (see sections 4.4 and 5.2).

In patients with reduced kidney function, the dose does not have to be adjusted (see section 5.2).

Safety and efficacy in children have not been determined.

4.3 Contraindications

- The use of intrathecal route is contra-indicated
- Known hypersensitivity to vinorelbine or other vinca alkaloids
- Neutrophil granulocytes <1500/mm³ or serious current or recent infection (within 2 weeks)
- Platelet count below 75 000/mm³
- Severe hepatic impairment not related to the tumoural process
- In combination with yellow fever vaccine (see section 4.5)
- Breast-feeding should be discontinued during treatment with vinorelbine (see section 4.6)
- Women of childbearing potential not using effective contraception (see section 4.6)

4.4 Special warnings and precautions for use

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.

• 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 75,000/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.

• Special caution is advised in patients with a history of ischaemic heart disease.

• The clinical relevance of impaired drug elimination capacity of the liver has not been characterised. Therefore no exact dose recommendation could be given. However in the pharmacokinetic study the highest administered dose in patients with severe liver dysfunction was 20 mg/m² (see section 5.2). For patients with severe hepatic impairment caution is recommended and careful monitoring of haematological parameters is required.

• Vinorelbine 10 mg/ml concentrate for solution for infusion should not be given concomitantly with radiotherapy if the treatment plan includes the liver.

• Vinorelbine 10 mg/ml concentrate for solution for infusion must not get into contact with the eye; 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 ophtalmologist.

• Strong inhibitors or inducers of CYP3A4 can affect the vinorelbine concentration and caution should therefore be exercised (see section 4.5).

• This product is generally not recommended in combination with live attenuated vaccines.

• For information on pregnancy, breastfeeding and fertility, please refer to section 4.6.

• To avoid the risk of bronchospasm - especially in combination therapy with mitomycin C appropriate prophylaxis may be considered. Outpatients should be informed that in case of dyspnea a doctor has to be informed.

• Because of the low level of renal excretion, there are no pharmacokinetic grounds for reducing the dose in patients with renal impairment.

4.5 Interaction with other medicinal products and other forms of interaction

The combination of vinorelbine and other drugs with known bone marrow toxicity is likely to increase the myelosuppressive adverse reactions.

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 affect the concentration of vinorelbine (see section 4.4). Vinorelbine is a substrate for P-glycoprotein and concurrent treatment with other drugs that inhibit (i.e. ritonavir, clarithromycin, cyclosporine, verapamil, quinidine) or induce (see list of CYP 3A4 inducers given above) the same transport protein can affect the concentration of vinorelbine.

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

Concomitant administration of vinca alkaloids and mitomycin C may increase the risk of bronchospasm (see also sections 4.4 and 4.8).

Concomitant use of phenytoin and vinorelbine is not recommended. The risk of exacerbation of convulsions may result from vinorelbine induced decrease in gastro-intestinal phenytoin absorption. Also, increased toxicity due to metabolites and/ or reduced efficacy of vinorelbine may result from phenytoin induced increase of hepatic metabolisation of vinorelbine.

Itraconazole: Concomitant use is not recommended due to potential increased neurotoxicity.

Ciclosporine, Tacrolimus: Excessive immunosuppression with risk of lymphoproliferation is to be taken into consideration.

Interactions common to all cytotoxics:
Due to the increased thrombotic risk in patients with cancer, the use of anticoagulation treatment is frequent. The high intra-individual variability of the coagulation status during diseases and the possibility of interaction between oral anticoagulants and anticancer chemotherapy require increased frequency of INR (International Normalised Ratio) monitoring, if it is decided to treat the patient with oral anticoagulants.

Concomitant use contraindicated: Yellow fever vaccine: risk of fatal generalised vaccinale disease (see section 4.3).

Concomitant use not recommended: Live attenuated vaccines (except yellow fever): risk of systemic, possibly fatal, disease. The risk is increased in subjects who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where it exists (poliomyelitis) (see section 4.4).

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 embryo- and feto-lethal and teratogenic (see section 5.3). During pregnancy Vinorelbine 10 mg/ml concentrate for solution for infusion should not be used unless clearly necessary. Fertile women should use effective methods of contraception during treatment with Vinorelbine 10 mg/ml concentrate for solution for infusion and should inform their doctor if they become pregnant. 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 also be considered.

- Breast-feeding
It is not known whether vinorelbine passes into the breast-milk. Breast-feeding must be discontinued before treatment with Vinorelbine 10 mg/ml concentrate for solution for infusion is commenced.

- Fertility
Vinorelbine can have genotoxic effects. Therefore, men being treated with vinorelbine are advised not to father a child during and for up to 6 months (minimum 3 months) following cessation of treatment.
Women of childbearing potential must use an effective contraception during 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 ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The undesirable effects that have been reported in more than isolated cases are listed below after organ system and frequency.
Undesirable effects are ranked under heading of 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, adverse reactions are ranked in order of decreasing seriousness.

Infections and infestations	Common: Infection bacterial, viral or fungal at different sites Uncommon: Severe sepsis with other visceral failure Rare: Septicaemia Very rare: Septicaemia complicated, septicaemia fatal
Blood and lymphatic system disorders	Very common: Neutropenia (grade 3:24.3% and grade 4:27.8% in monotherapy), anaemia (grade 3 – 4: 7.4 % in monotherapy) Common: Thrombocytopenia (grade 3 – 4: 2,5 %), febrile neutropenia, neutropenic sepsis with potential fatal outcome in 1.2% of cases
Immune system disorders	Common: Allergic reactions (skin reactions, respiratory reactions) Rare: systemic allergic reactions (anaphylaxis, angioedema)
Metabolism and nutrition disorders	Uncommon: Hyponatraemia Very rare: Inappropriate antidiuretic hormone secretion (SIADH)
Nervous system disorders	Very common: Neurological disorders (grade 3: 2.6 %; G4: 0.1 %), Constipation (grade 3-4: 2.7% in monotherapy, grade 3-4: 4.1% in combination therapy) (see also „Gastrointestinal disorders“), loss of deep tendon reflexes Common: Paraesthesia with sensory and motor symptoms Uncommon: Paralytic ileus (see also “Gastrointestinal disorders”) Rare: Weakness of lower extremities Very rare: Guillain-Barré syndrome
Cardiac disorders	Rare: Ischaemic heart disease such as angina pectoris, transitory electrocardiogram changes, myocardial infarction Very rare: Tachycardia, palpitation and heart rhythm disorders
Vascular disorders	Uncommon: Hypotension, hypertension, flushing and peripheral coldness. Rare: Severe hypotension, collapse
Respiratory, thoracic and mediastinal disorders	Common: Dyspnoea, bronchospasm Rare: Interstitial lung disease Very rare: Respiratory insufficiency

Gastrointestinal disorders	Very common: Constipation (grade 3-4: 2.7% in monotherapy, grade 3-4: 4.1% in combination therapy) (see also “Nervous system disorders”), nausea, vomiting (grade 3-4: 2.2% in monotherapy), diarrhoea, stomatitis, oesophagitis, anorexia Uncommon: Paralytic ileus (see also “Nervous system disorders”) Rare: Pancreatitis
Hepatobiliary disorders	Very common: Abnormal liver function values (total bilirubin increased, alkaline phosphatase increased, aspartate aminotransferase increased, alanine aminotransferase increased)
Skin and subcutaneous tissue disorders	Very common: Alopecia (grade >2: 4.1% in monotherapy) Common: Skin reactions
Musculoskeletal and connective tissue disorders	Common: Myalgia, Arthralgia Rare: Jaw pain
Renal and urinary disorders	Common: Creatinine increased
General disorders and administration site conditions	Very common: Fatigue, fever, pain in different locations, asthenia, injection site erythema, pain, discolouration and phlebitis Rare: Injection site necrosis

4.9 Overdose

Overdosages may produce severe bone marrow depression with fever and infection, paralytic ileus have also been reported. Symptomatic treatment with blood transfusion and broad-spectrum antibiotic therapy is recommended. There is no specific antidote.

As there is no specific antidote for the overdosage of vinorelbine given intravenously, symptomatic measures are necessary in case of an overdosage, e.g.:
- Continuous control of vital signs and careful monitoring of the patient;
- Daily control of blood count to observe the need of blood transfusions, of growth factors and to detect the need of intensive care and to minimize the risk of infections;
- Measures for prevention or for therapy of paralytic ileus;
- Control of circulation system and of liver function;
- Broad spectrum antibiotic therapy may be necessary in case of complications due to infections.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents (vinca alkaloids),
ATC code: L 01 CA 04

Vinorelbine is a cytostatic drug of the vinca alkaloid family.
Vinorelbine inhibits tubulin polymerisation and binds preferentially to mitotic microtubules, only affecting axonal microtubules at high concentrations. The induction of the tubulin spiralization is less than that produced by vincristine.

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

5.2 Pharmacokinetic properties

Pharmacokinetic parameters of vinorelbine were evaluated in blood.

Distribution
The stady-state volume of distribuition is large, on average 21.2 l/h/Kg (range 7.5 – 39.7 l/h/Kg), which indicates extensive tissue distribution.

Vinorelbine has high affinity for platelets and lymphocytes. Binding to plasma proteins is low (13.5% of the total blood-bound vinorelbine). 78% of the total blood-bound vinorelbine was associated with platelets and 4.8% of the total blood-bound vinorelbine was associated with lymphocytes.

There is significant uptake of vinorelbine in the lungs, as assessed by surgical lung biopsies, which showed concentrations up to 300-fold higher than in serum. Vinorelbine is not found in the central nervous system.

Biotransformation
Vinorelbine is principally metabolised by cytohrome P450 3A4. All metabolites have been identified and none is active, except 4-O-deacetyl vinorelbine, which is the main metabolite in blood. No sulphonic or glucuronic conjugates are found.

Elimination
The mean terminal half-life of vinorelbine is around 40 hours. Blood clearance is high, approching hepatic blood flow, and is 0.72 l/h/Kg on average (range: 0.32 – 1.26 l/h/Kg).

Renal elimination is low (< 20% of the intravenous dose administered) and consists mostly of the in parent compound. Biliary excretion is the predominant elimination route of unchanged vinorelbine, which is the main recovered compound, and its metabolite 4-O-deacetyl vinorelbine.

Special patient groups
Renal impairment
The effects of renal dysfunction on the vinorelbine disposition have not been assessed. However, dose reduction in case of reduced renal function is not indicated due to the low renal elimination.

Liver impairment
A first study has reported the effects of liver impairment on vinorelbine pharmacokinetics. This study was performed in patients with hepatic metastases due to breast cancer, and concluded that a change in 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 dysfunction (Bilirubin < 2 x UNL and Transaminases < 5 x UNL) treated up to 25 mg/m² and 8 patients with severe dysfunction (Bilirubin > 2 x UNL and/or Transaminases > 5 x UNL) treated up to 20 mg/m². Mean total clearance in these two subsets of patients was similar to that in patients with normal hepatic function. Therefore, the pharmacokinetics of vinorelbine are not modified in patients presenting with moderate or severe liver impairment.
These data may however not be representative for patients with reduced drug elimination capacity of the liver and therefore caution is recommended in patients with severe hepatic impairment and careful monitoring of haematological parameters is required (see sections 4.2 and 4.4).

Eldery patients
Study on oral vinorelbine in eldery patients (≥ 70 years) with NSCLC demonstrated there is no influence of the age on vinorelbine pharmacokinetics and that no dose reduction is required.

PK-PD relation
A strong relationship has been demonstrated between vinorelbine blood exposure and of leucocytes or PMNs decreases.

5.3 Preclinical safety data

Mutagenic and carcinogenic potential
In animal studies, vinorelbine induced aneuploidy and polyploidy. It can be assumed that vinorelbine can also cause genotoxic effects in humans (induction of aneuploidy and polyploidy).
The results of studies for carcinogenic potential in mice and rats were negative but only low doses have been tested.

Reproductive toxicity studies
In animal reproductive studies, effects were observed at subtherapeutic dosages. Embryo and fetotoxicity were seen, such as intra-uterine growth retardation and delayed ossification. Teratogenicity (fusion of the vertebrae, missing ribs) was observed at maternally 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 the monkey did not reveal any adverse effect on the cardio-vascular system.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

6.2 Incompatibilities

- Vinorelbine 10 mg/ml concentrate for solution for infusion should not be diluted with 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

Before first opening: 2 years.
After dilution: Immediate use.
Chemical and physical in use stability has been demonstrated for 24 hours at 2-8°C and at 25°C.
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 not normally be longer than 24 hours at 2-8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2ºC - 8ºC). Do not freeze.
Store the vial in the outer carton in order to protect from light.
For storage condition of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Neutral, type I clear glass vials, with grey elastomer stoppers covered by blue aluminium cap with 1 ml and with 5 ml of concentrate.

Pack sizes :
1 ml of concentrate for solution for infusion : 1 vial
5 ml of concentrate for solution for infusion : 1 vial

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only, discard any unused contents.
Before being administered, the solution for infusion must be inspected visually to detect the possible presence of particles or discoloration.
The preparation and administration of vinorelbine should be carried out only by trained personnel.
Personnel must be provided with appropriate handling materials, notably long sleeved gowns, protection masks, caps, protective goggles, sterile single-use gloves, protective covers for the work area and collection bags for waste.
Spills and leakages must be wiped up.
Syringes and infusion sets should be assembled carefully to avoid leakage (use of Luer lock fittings is recommended).
Excreta and vomit must be handled with care.
Precautions should be taken to avoid exposing staff during pregnancy.
All contact with the eyes must be strictly avoided. Immediate washing of the eye with normal saline solution should be undertaken if any contact occurs. In case of irritation an ophthalmologist should be contacted.
After preparation, any exposed surface must be thoroughly cleaned and hands and face washed.
There is no incompatibility between the contents and container for Vinorelbine 10 mg/ml concentrate for solution for infusion and a neutral glass bottle, PVC bag, vinylacetate bag or infusion set with PVC tubes.
It is recommended to administer vinorelbine as an infusion over the course of 5-10 minutes after dilution in 20-50 ml physiological 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. After administration the vein must be flushed through thoroughly with at least 250 ml isotonic solution.

Vinorelbine 10 mg/ml concentrate for solution for infusion 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 Vinorelbine 10 mg/ml concentrate for solution for infusion 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.

Unused medicinal product and waste must be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 1226/10/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT