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 concentrate for solution for infusion contains 10mg vinorelbine equivalent to 13.85mg vinorelbine tartrate.
Each 1 ml vial contains 10 mg vinorelbine (as tartrate).
Each 5 ml vial contains 50 mg vinorelbine (as tartrate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, colourless to slightly yellow solution with a pH of 3.3 to 3.8

Diluted product: the osmolarity of the diluted product is about 330 mOsm/l.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Vinorelbine is indicated in the treatment of:
- Non-small cell lung cancer (stage 3 or 4).
- As single agent to 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 should be administered under the supervision of a physician with extensive experience in therapy with cytostatics.

Strictly intravenous administration after appropriate dilution.
Intra-thecal administration of vinorelbine may be fatal.
Instructions for use and handling: refer to section 6.6.

Vinorelbine 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 with at least 250 ml of an isotonic solution infusion to flush the vein.

Non-small cell lung cancer
As a single agent the normal dose is 25-30mg/m², administered once weekly. In polychemotherapy the schedule regimen is a function of the protocol. The normal dose could be used (25-30mg/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/m² body surface area.

- **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 impairment**
The pharmacokinetics of vinorelbine is not modified in patients presenting moderate or severe liver impairment. Nevertheless as a precautionary measure a reduced dose of 20mg/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 impairment**
In patients with reduced kidney function, the dose does not have to be adjusted (see section 5.2).

- **Administration in children**
Safety and efficacy in children have not been established and administration is therefore not recommended.

4.3 Contraindications

- Known hypersensitivity to vinorelbine or other vinca alkaloids, or to any of theexcipients.
- Neutrophil count < 1500/mm^3 or severe infection current or recent (within 2 weeks)
- Platelet count < 100000/mm^3
- Pregnancy (see section 4.6)
- Breast-feeding should be discontinued during treatment with vinorelbine (see Section 4.6).
- Women of childbearing potential not using effective contraception (see Sections 4.4 and 4.6).
- In combination with yellow fever vaccine (see section 4.5)

4.4 Special warnings and precautions for use

Special warnings

Strictly for intravenous use only.

Vinorelbine should be administered under the supervision of a physician experienced in the use of chemotherapy .

Since inhibition of the hematopoietic system is the main risk associated with vinorelbine, close haematological monitoring should be undertaken during treatment (determination of hemoglobin level and the leukocyte, neutrophil and platelet counts on the day of each new administration).

The dose limiting adverse reaction is mainly neutropenia. This effect is non-cumulative, having its nadir between 7 and 14 days after the administration and is rapidly reversible within 5 to 7 days. If the neutrophil count is below 1500/$mm^3$and/or the platelet count is below 100000/mm^3, then the treatment should be delayed until recovery.

If patients present signs or symptoms suggestive of infection, a prompt investigation should be carried out.

Special precautions for use

Special care should be taken when prescribing for patients with history of ischemic heart disease (refer to 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, refer to 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.

Refer to section 4.2.

Vinorelbine should not be given concomitantly with radiotherapy if the treatment field includes the liver .

This product is specifically contra-indicated with yellow fever vaccine and its concomitant use with other live attenuated vaccines is not recommended.
Combination of vinorelbine and strong inhibitors or inducers of CYP3A4 is not recommended (see section 4.5)

All contact with the eyes should be strictly avoided: there is a risk of severe irritation and even corneal ulceration if the drug is sprayed under pressure. Immediate washing of the eye with sodium chloride 9mg/ml (0.9%) solution for injection should be undertaken if any contact occurs and contact an ophthalmologist.

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 dyspnoea a doctor has to be informed.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions specific to vinorelbine:

- 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 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. Caution should be exercised when combining Vinorelbine with strong modulators of this membrane transporter.

- There is no mutual pharmacokinetic interaction when combining vinorelbine with cisplatin over several cycles of treatment. However, the incidence of granulocytopenia associated with vinorelbine use in combination with cisplatin is higher than associated with vinorelbine single agent.

Interactions specific to vinca-alkaloids:

- Concomitant use to take into consideration:

  Mitomycin C: risk of bronchospasm and dyspnoea are increased, in rare case an interstitial pneumonitis was observed.

Interactions common to all cytotoxics:

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

- Concomitant use contraindicated:

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

- Concomitant use not recommended:

Live attenuated vaccines (for yellow fever vaccine, see concomitant use contraindicated): risk of generalised vaccine disease, possibly fatal. This risk is increased in patients already immunodepressed by their underlying disease. It is recommended to use an inactivated vaccin when exists (poliomyelitis) (refer to section 4.4).

Phenytoin: risk of exacerbation of convulsions resulting from decreased gastrointestinal absorption of phenytoin by vinorelbine.

- Concomitant use to take into consideration:

Ciclosporine, tacrolimus: excessive immunodepression with risk of lymphoproliferation

4.6 Fertility, pregnancy and lactation

Pregnancy
Vinorelbine is suspected to cause serious birth effects when administered during 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).
Vinorelbine is contraindicated in pregnancy: see section 4.3.
Fertile women should use effective methods of contraception during treatment with vinorelbine and should inform their doctor if they become pregnant.
In case of a vital indication for treatment with Vinorelbine during pregnancy a medical consultation concerning the risk of harmful effects for the child should be conducted and the patient should be monitored carefully.
If pregnancy occurs during treatment genetic counselling should be offered.

Breast-feeding
It is not known whether vinorelbine passes into the breast milk. The excretion of vinorelbine in milk has not been studied in animal studies. Breast-feeding must be discontinued before treatment with vinorelbine 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 method of contraception during treatment and up to 3 months after 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 but on the basis of the pharmacodynamic profile vinorelbine does not affect the ability to drive and use machines. However, caution is necessary in patient treated with vinorelbine considering some adverse effects of the drug.

4.8 Undesirable effects

Adverse reactions reported as more than isolated cases are listed below, by system organ class and by frequency. *Frequencies are defined as:* 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), according to the MedDRA frequency convention and system organ classification.

The most commonly reported adverse drug 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 from Post Marketing experience has been added according to the MedDRA classification with the frequency *Not known*

Detailed Adverse reactions information:

Reactions were described using the W.H.O 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: Infection bacterial, viral or fungal at different sites (respiratory, urinary, GI tract) mild to moderate and usually reversible with an appropriate treatment.* *Uncommon: Severe sepsis with other visceral failure Septicaemia* *Very rare: Complicated septicaemia and sometimes fatal* *Not known: Neutropenic sepsis*
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 are seldom severe* *Not known: Febrile neutropenia*
Immune system disorders	*Not known: Systemic allergic reactions as anaphylaxis, anaphylactic shock or anaphylactoïd type reaction*
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 has been reported after a prolonged chemotherapy* *Uncommon: Severe paraesthesias with sensory and motor symptoms are infrequent* *Very rare: Guillain Barre Sydrome* *These effects are generally reversible.*
Cardiac disorders	*Rare: Ischaemic heart disease (angina pectoris, 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	*Uncommon: Dyspnoea and bronchospasm may occur in association with Vinorelbine treatment as with other vinca alkaloids* *Rare: Interstitial pneumopathy has been reported in particular in patients treated with Vinorelbine Strides in combination with mitomycin*
Gastrointestinal disorders	*Very common: Stomatitis (G1-4: 15% with Vinorelbine as single agent); Nausea and vomiting (G 1-2: 30.4% and G 3-4: 2.2%); Anti-emetic therapy may reduce their occurrence.* *Constipation is the main symptom (G 3-4: 2.7%) which rarely progresses to paralytic ileus with Vinorelbine as*

	single agent and (G3-4: 4.1%) with the combination of Vinorelbine and other chemotherapeutic agents. *Diarrhoea and oesophagitis.* *Rare: Paralytic ileus, treatment may be resumed after recovery of normal bowel mobility ; Pancreatitis have been reported*
Hepatobiliary disorders	*Very common: Transient elevations of liver function tests (G 1-2) without clinical symptoms were reported (SGOT in 27.6% and SGPT in 29.3%).*
Skin and subcutaneous tissue disorders	*Very common: Alopecia, usually mild in nature, may occur (G3-4: 4.1% with Vinorelbine as single chemotherapeutic agent).* *Rare: Generalized cutaneous reactions have been reported with Vinorelbine* *Not known: Erythema on hands and feet*
Musculoskeletal and connective tissue disorders	*Common: Arthralgia including jaw pain and myalgia*
Renal and urinary disorders	*Common: Creatinine increased*
General disorders and administration site conditions	*Very common: Reactions at the injection site may include erythema, burning pain, Vein discoloration and local phlebitis (G 3-4: 3.7% with Vinorelbine as single chemotherapeutic agent).* *Common: Asthenia, fatigue, fever, pain at different locations including chest pain and pain at the tumour site have been experienced by patients receiving Vinorelbine therapy.* *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.*

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, growth factors and broad-spectrum antibiotic therapy is recommended. There is no known 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 and analogues, ATC code: L01CA04
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 concentration. The induction of tubulin spiralization is less than that produced by vincristine. Vinorelbine blocks mitosis at 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 steady-state volume of distribution is large, on average 22.2 $l.kg^{-1}$ (range: 7.5-39.7 $l.kg^{-1}$), which indicates extensive tissue distribution.. Binding to plasma protein is low (13.5%). However, vinorelbine binds strongly to blood cells and especially to platelets. 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
All metabolites of vinorelbine are formed by CYP 3A4 isoform of cytochromes P450, except 4-O-deacetylvinorelbine likely to be formed by carboxylesterases. 4-O-deacetylvinorelbine is the only active metabolite and the main one observed in blood.

Neither sulfate nor glucuronide conjugates are 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 in parent compound. Biliary excretion is the predominant elimination route of unchanged vinorelbine, which is the main recovered compound, and its metabolites.

Special patient groups

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

Liver impairment
A study has reported the effects of liver impairment on vinorelbine pharmacokinetics in patients with liver metastases due to breast cancer. From this study it was concluded that change in mean clearance of vinorelbine was only observed when more than 75% of the liver is involved.

Furthermore 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 an/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 is not modified in patients presenting moderate or severe liver impairment. Nevertheless, as a precautionary measure a reduced dose of 20mg/m² and close monitoring of hematological parameters is recommended in patient 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 pharmacokinetics of vinorelbine were not influenced by age. However, since elderly patients are frail, caution should be exercised when increasing the dose of vinorelbine see section 4.2.

Pharmacokinetic/pharmacodynamic relationships
A strong relationship has been demonstrated between vinorelbine blood exposure and of leucocytes or polymorphonuclear leucocytes 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 (aneuploidy and polyploidy). The results for carcinogenic potential in the mouse and rat were negative but only low doses have been tested.

Reproductive toxicity studies
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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections.

6.2 Incompatibilities

Vinorelbine should not be diluted in alkaline solutions (risk of precipitation).

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, except those mentioned in section 6.6.

6.3 Shelf life

Unopened
2 years.

After first opening
The content of the vial should be used immediately after the first opening of vial.

Shelf-life after dilution
Following dilution with physiological sodium chloride solution or 50 mg/mL (5%) glucose solution, the chemical and

physical stability of the reconstituted solution has been confirmed for 24 hours at 2 – 8°C and not above 25°C at concentrations from 0.5 mg/ml to 3.0 mg/ml.

From a microbiological point of view the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

As packaged for sale
Store in a refrigerator (2°C - 8°C). Keep 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

1ml vial: Colourless glass vial (type I) with a grey bromobutyl rubber stopper and sealed with a light blue flip off aluminium seal.

5ml vial: Colourless glass vial (type I) with a grey bromobutyl rubber stopper and sealed with a light blue flip off aluminium seal.

Pack-sizes:
1 x 1 ml vial
1 x 5 ml 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.

Handling and use
The preparation and administration of injectable solutions of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicines used, in conditions that guarantee the protection of the environment and, in particular, the protection of the personnel handling the medicines. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or drink in this area.

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.

Syringes and infusion sets should be assembled carefully to avoid leakage (use of Luer lock fittings is recommended).

Spills and leakages must be wiped up, wearing protective gloves.

Precautions should be taken to avoid exposing staff during pregnancy.

All contact with 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.

In case of skin contact, the affected area should be thoroughly washed with water.

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

Preparation of the solution for infusion
There is no incompatibility between Vinorelbine Strides and glass vials, PVC bag, vinyl acetate bag or polypropylene syringe.

In case of polychemotherapy, Vinorelbine Strides should not be mixed with other agents.

The intra-thecal route is contraindicated: see sections 4.2 and 4.4

Vinorelbine must only be administered by the intravenous route as an infusion.

Vinorelbine 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 with at least 250 ml of a isotonic solution infusion to flush the vein.

Vinorelbine 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 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.

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

7 MARKETING AUTHORISATION HOLDER

Generics (UK) Limited
Station Close
Potters Bar
Hertfordshire EN6 1TL
UK

8 MARKETING AUTHORISATION NUMBER

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