Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vinorelbine Teva 10 mg/ml, concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL of solution contains 10 mg vinorelbine (as vinorelbine tartrate)

Each 1 ml vial contains 10 mg of vinorelbine (as tartrate).
Each 5 ml vial contains 50 mg of vinorelbine (as tartrate).

For a full list of the excipients, see section 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear solution from colorless to pale yellow and free from visible particles.
pH: Between 3.3 and 3.8

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 route only.

Vinorelbine Teva should be given in cooperation with a physician with extensive experience in therapy with cytostatics. The use of intrathecal route is contra-indicated. Intra-thecal administration of vinorelbine may be fatal.

For instructions regarding use and handling, see section 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 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 usual dose is 25 - 30 mg/m², administered once weekly.
In polychemotherapy, the schedule regimen is 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.

Advanced or 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.

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 patients with severe liver impairment. (see 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.

4.3 Contraindications

This medicinal product is contraindicated in the following cases:

- Known hypersensitivity to vinorelbine or other vinca alkaloids, or to any of the constituents
- Neutrophil count <1500/mm^3 or serious infection, current or recent (within 2 weeks)
- Platelet count < 100 000/mm^3
- Pregnancy (see section 4.6)
- Lactation (see section 4.6)
- In combination with yellow fever vaccine (see section 4.5).

4.4 Special warnings and precautions for use

Special warnings

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

Since the inhibition of the haematopoietic system is the main risk associated with vinorelbine, close haematological monitoring should be undertaken during treatment (determination of haemoglobin level and 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 patient presents 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 (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).

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 liver attenuated vaccines is not recommended.

Caution must be exercised when combining vinorelbine with phenytoin, fosphenytoins (like all cytotoxics) and with itraconazole or posaconazole (like all vinca-alkaloids) is not recommended (see section 4.5).

All contact with 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.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use contraindicated
Yellow fever vaccine: risk of fatal generalised vaccine disease (see 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 vaccine when one exists (e.g. poliomyelitis) (see section 4.4).

Phenytoin (and fosphenytoins): risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic drug or risk of toxicity enhancement or loss of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin.

Concomitant use that should be taken with caution:
Vitamin K antagonists : Increase of the thromboembolic and hemorrhage risk during the cancer disease. In addition, a possible interaction between cytotoxics and vitamin K antagonists cannot be ruled out.
Therefore the INR monitoring should be more frequently made.

Concomitant use to take into consideration
Immunosupressants: excessive immunodepression with risk of lymphoproliferation.

Interactions specific to vinca-alkaloids

Concomitant use not recommended
Itraconazole, posaconazole: increased neurotoxicity of vinca- alkaloids due to the decrease of their hepatic metabolism.

Concomitant use to take with caution:
Protease inhibitors: increased toxicity of vinca- alkaloids due to the decrease of their hepatic metabolism. A close clinical monitoring should be exercised and, possibly, a dosage adjustment of vinorelbine.

Concomitant use to take into consideration
Mitomycin C: risk of bronchospasms and dyspnoea are increased, in rare case an interstitial pneumonitis was observed.

Interactions specific to vinorelbine

- The combination of vinorelbine with other drugs known for their bone marrow toxicity is likely to exacerbate the myelosuppressive side effects.

- 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.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/Contraception in males and females
Women of child-bearing potential must use effective contraception during treatment and up to 3 months after treatment.

Pregnancy
Vinorelbine is suspected to cause birth defects when administered during pregnancy. Vinorelbine is contraindicated in pregnancy (see section 4.3).

In case of a vital indication a medical consultation concerning the risk of harmful effects for the child should be performed for the therapy of a pregnant patient. If pregnancy occurs anyhow during treatment, genetic counselling should be offered.

Breast-feeding
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 suckling child cannot be excluded therefore breast feeding must be discontinued before starting treatment with vinorelbine (see section 4.3).

Fertility
Men being treated with vinorelbine are advised not to father a child during and minimally up to 3 months after treatment. Prior to treatment advice should be sought for conserving sperm due to the chance of irreversible infertility as a consequence of treatment 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

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, < 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 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 have 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).

List of adverse reactions

Infections and infestations	*Common:* *Infection bacterial, viral or fungal at different localization (respiratory, urinary, GI tract…) mild to moderate and usually reversible with an appropriate treatment.* *Uncommon:*

	Severe sepsis with other visceral failure *Septicaemia* *<u>Very rare:</u>* *Complicated septicaemia and sometimes fatal* *<u>Not known:</u>* *Neutropenic sepsis*
Blood and lymphatic system disorders	*<u>Very common</u>* *Bone marrow depression resulting mainly in neutropenia (G 3:24.3% and G 4:27.8%),reversible within 5 to 7 days and non –cumulative over time* *Anaemia (G 3 – 4: 7.4 % in monotherapy)* *<u>Common</u>* *Thrombocytopenia (G3 – 4: 2.5 %) may occur but are seldom severe* *<u>Not known</u>* *Febrile neutropenia*
Immune system disorders	*<u>Not known</u>* *Systemic allergic reactions as anaphylaxis, anaphylactic shock or anaphylactoid type reaction*
Endocrine disorders	*<u>Not known</u>* *Inappropriate antidiuretic hormone secretion (SIADH)*
Metabolism and nutrition disorders	*<u>Rare</u>* *Severe hyponatraemia* *<u>Not known</u>* *Anorexia*
Nervous system disorders	*<u>Very common</u>* *Neurological disorders (G 3-4: 2.7 %) including loss of deep tendon reflexes* *Weakness of the lower extremities has been reported after a prolonged chemotherapy* *<u>Uncommon</u>* *Severe paresthesias with sensory and motor symptoms are infrequent* *These effects are generally reversible*
Cardiac disorders	*<u>Rare</u>* *Ischaemic heart disease (angina pectoris, myocardial infarction)* *<u>Very rare</u>* *Tachycardia, palpitation and heart rhythm disorders*
Vascular disorders	*<u>Uncommon</u>* *Hypotension, Hypertension, Flushing and peripheral coldness.* *<u>Rare</u>* *Severe hypotension, Collapse*
Respiratory, thoracic and mediastinal disorders	*<u>Uncommon</u>* *Dyspnoe and bronchospasm may occur in association with vinorelbine treatment as with other vinca alkaloids* *<u>Rare</u>* *Interstitial pneumopathy has been reported in particular in patients treated with vinorelbine in combination with mitomycin*
Gastrointestinal disorders	*<u>Very common</u>* *Stomatitis (G1-4: 15% with vinorelbine as single agent)* *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 as single agent and (G3-4: 4.1%) with*

	the combination of vinorelbine and other chemotherapeutic agents *Common* *Diarrhoea usually mild to moderate may occur* *Rare* *Paralytic ileus, treatment may be resumed after recovery of normal bowel mobility* *Pancreatitis has been reported*
Hepatobiliary disorders	*Very common* *Transient elevations of liver function tests (G1-2) 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* *Generalised 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*
General disorders and administration site conditions	*Very common* *Reactions at the injection site may include erythema, burning pain, vein discoloration and local phlebitis (G3-4: 3.7% with vinorelbine as single chemotherapeutic agent)* *Common* *Asthenia, fatigue, fever, pain at different location 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 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), ATC code: L01 CA04

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

5.2 Pharmacokinetic properties

Following an intravenous injection by bolus or infusion, the blood concentrations of vinorelbine decrease in a tri-exponential manner with a slow terminal elimination phase.
The mean pharmacokinetic parameters of vinorelbine are evaluated on the total blood. The elimination half-life is approximately 38 hours. Total clearance is high: 0.72 L/h/kg (extremes: 0.32–1.26 L/h/kg) and close to the hepatic blood flow rate. The steady state distribution volume is large: 21.2 L/kg (extremes: 7.5–39.7 L/kg) characterising high tissue distribution. In particular, the penetration of vinorelbine in the pulmonary tissues seems to be high, as is reflected by the mean ratio of tissue/plasma concentrations, detected by pulmonary surgical biopsy, which is greater than 300. Vinorelbine has not been detected in the central nervous system. Blood exposure increases in proportion to the dose. The linearity of the pharmacokinetics of vinorelbine has been demonstrated up to the dose level of 45 mg/m^2.

Its rate of binding to plasma proteins is low (13.5%). Vinorelbine is highly bound to blood cells, particularly platelets (78%).

Vinorelbine is metabolised mainly by the isoform CYP3A4 of cytochromes P450. All metabolites have been identified, and none of them is active except for 4-0-deacetyl-vinorelbine, which is the primary metabolite detected in the blood.

The metabolism of vinorelbine does not involve glucoroconjugation or sulfoconjugation.

Biliary excretion is the predominant route of elimination, in the form of vinorelbine and metabolites. Unchanged vinorelbine is the main component.
Renal elimination is low (< 20% of the dose) and takes place mainly in unchanged form.

Although the impact of renal dysfunction on the elimination of vinorelbine has not been evaluated, there is no reason to reduce the dosage in patients with renal failure, because the renal elimination of vinorelbine is low.
The effect of hepatic failure on the pharmacokinetics of vinorelbine was first studied in patients with hepatic metastases secondary to breast cancer. The study concluded that a change in clearance was only observed when the level of hepatic invasion was greater than 75%. Moreover, a phase I study has been conducted in patients with impaired hepatic function: 6 patients with moderate hepatic failure (serum bilirubin > 2 times ULN and transaminases < 5 times ULN) treated with the maximum dose of 25 mg/m^2 and 8 patients with severe hepatic failure (serum bilirubin > 2 times ULN and transaminases > 5 times ULN) treated with the maximum dose of 20 mg/m^2. Total clearance in these patients was similar to that of patients with normal hepatic function, and demonstrated that the pharmacokinetics of vinorelbine was not changed in the event of hepatic failure, irrespective of the degree.
A strong correlation was established between blood exposure to vinorelbine, leucopoenia and neutropenia.

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 pharmacological studies performed in the dog and 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

This medicinal product should not be mixed with other medicinal products except for those mentioned in section 6.6.

6.3 Shelf life

Before opening: 18 months

After first opening/dilution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the product must be used immediately.

6.4 Special precautions for storage

Store in the refrigerator (2°C - 8°C). Do not freeze. Store in the original package in order to protect from light.

6.5 Nature and contents of container

1 ml in vial (type I glass) with a stopper (chlorobutyl rubber) with a seal (aluminium)
5 ml in vial (type I glass) with a stopper (chlorobutyl rubber) with a seal (aluminium)

Pack sizes :
1 ml of concentrate for solution for infusion : 1 vial
1 ml of concentrate for solution for infusion : 10 vials
5 ml of concentrate for solution for infusion : 1 vial
5 ml of concentrate for solution for infusion : 10 vials

Vials may be sheathed in protective sleeves.

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 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.

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.

There is no incompatibility between Vinorelbine Teva and glass vials, PVC bag, polyethylene vial or polypropylene syringe.

Vinorelbine Teva 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.

Vinorelbine Teva 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 Teva 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.

In the event of accidental contact with the eye, immediately wash the eye thoroughly.

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

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10
3542 Dr Utrecht
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 749/86/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 9th January 2009

10 DATE OF REVISION OF THE TEXT

August 2014