VINORELBINE 10MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION
PL 00289/0808

UKPAR

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LAY SUMMARY

The MHRA today granted Teva UK Limited a Marketing Authorisation (licence) for the medicinal product Vinorelbine 10mg/ml Concentrate for Solution for Infusion (PL 00289/0808). This is a prescription only medicine (POM) for the treatment of cancer, specifically advanced non-small cell lung cancer and advanced breast cancer.

Vinorelbine 10mg/ml Concentrate for Solution for Infusion contains the active ingredient vinorelbine tartrate, which causes cancer cells to die.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Vinorelbine 10mg/ml Concentrate for Solution for Infusion outweighed the risks, hence a Marketing Authorisation has been granted.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a marketing authorisation for the medicinal product Vinorelbine 10mg/ml Concentrate for Solution for Infusion to Teva UK Limited (PL 00289/0808) on 13th August 2007. The product is a prescription-only medicine.

The application was submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, as a generic product of the original product Navelbine 10mg/ml Concentrate for Solution for Infusion (Pierre Fabre Limited, UK).

The product contains the active ingredient vinorelbine tartrate. It is indicated as a single agent or in combination for the first-line treatment of stage 3 or 4 non-small cell lung cancer, and for the treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline-containing regimen.

Vinorelbine is a semi-synthetic member of the vinca alkaloids group of antineoplastic agents. Like other vinca alkaloids vinorelbine blocks polymerisation of the mitotic spindle and thereby arrests cell cycle progression in the G2 and M phases, resulting in cell death.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

RINN	Vinorelbine tartrate
Chemical Name:	Methyl (3aR,4R,5S,5aR,10bR,13aR)-4-(acetyloxy)-3a-ethyl-9[(8S)-4-ethyl-8-(methoxycarbonyl)-1,3,6,7,8,9-hexahydro-2H-methanoazacyclodecino[4,3-b]indol-8-yl]-5-hydroxy-8-methoxy-6-methyl-3a,4,5,5a,6,11,12,13a-octahydro-1H-indolizinol[8,1-cd]carbazol-5-carboxylate (2R,3S)-2,3-dihydroxybutanedioate Or: 3',4'-Didehydro-4'-deoxy-8'-norvincaleukoblastine ditartrate
Formula:	$C_{45}H_{54}N_4O_8 \cdot 2(C_4H_6)_6$
RMM:	1079.11
General properties:	White to almost white powder which is hygroscopic. Freely soluble in water and alcohol; practically insoluble in hexane.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis. No materials of animal or human origin are used in the production of the active substance.

An appropriate specification is provided for the active substance vinorelbine tartrate.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof of structure has been supplied for the active pharmaceutical ingredient.

All potential known impurities have been identified and characterised.

Batch analysis data are provided that comply with the proposed specification.

Active vinorelbine tartrate is stored in amber glass vessels with a low-density polyethylene lid and a polypropylene homopolymer screw cap. This is then placed in a plastic securibox. Dimensions of all containers and certification for the glass vessels and lids showing conformity with requirements for materials in contact with food.

Appropriate stability data have been generated. The data support a retest period of 36 months when active is stored at -20°C in hermetically sealed amber glass vessels and protected from light. A stability commitment has been made to continue the long term stability of the stability batches up to 60 months and then one batch per year.

DRUG PRODUCT

Other ingredients

Other ingredients consisted of pharmaceutical excipients water for injections (diluent) and nitrogen (for deoxygenation of water for injections and for the headspace gas in the vials).

All excipients used comply with their respective Ph Eur monograph. Satisfactory certificates of analysis have been provided for all excipients. None of the excipients used contain material of animal or human origin.

Essential similarity

The physico-chemical properties of the drug product have been compared with the originator product. Slight differences in the impurity profile were evident thought these are not considered to be a point of issue as levels are low. Essential similarity has been adequately demonstrated.

Manufacture

A description and flow-chart of the manufacturing method has been provided. A suitable batch formula has been provided for all pilot-scale and commercial-scale batches.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results appear satisfactory.

Finished product specification

The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

The finished product is supplied as 10mg in 1ml liquid and 50mg in 5ml liquid. The proposed container is a 2ml or 5ml clear glass (type I) vial sealed with a grey chlorobutyl rubber stopper and an aluminium cap with plastic flip-off seal.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. Some migration of palmitic acid and stearic acid was observed from the stopper to the solution, but the levels are low and can be considered safe.

All primary packaging is controlled to Ph Eur standards.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 36 months has been set (24 hours shelf life after opening), which is satisfactory. The precautions ‘Keep container in outer carton’, ‘Protect from light’ and ‘Store in refrigerator (2-8°C)’ have been included.

Conclusion

It is recommended that a Marketing Authorisation is granted for this application.

The requirements for a generic product of the proposed and originator products have been met with respect to qualitative and quantitative content of the active substance. In addition, similar physico-chemical properties have been demonstrated for the proposed and originator products.

PRECLINICAL ASSESSMENT

This is an application for a generic product of Navelbine 10mg/ml Concentrate for Solution for Infusion (Pierre Fabre Limited, UK), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for an application of this type.

CLINICAL ASSESSMENT

1. INDICATIONS

- As a single agent or in combination for the first line treatment of stage 3 or 4 non-small cell lung cancer.
- Treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen.

These are consistent with the indications for the reference product.

2. DOSE & DOSE SCHEDULE

Strictly by intravenous injection through an infusion line. Administration by other routes is fatal.

Administration should always be followed by a normal saline infusion to flush the vein. It is extremely important to make sure that the needle is correctly inserted into the vein before commencing the injection (see 4.4)

In adults:

- Vinorelbine is usually given at 25-30mg/m^2 weekly.
- Vinorelbine may be administered by slow bolus (5-10 minutes) after dilution in 20- 50 ml of normal saline solution or dextrose 5% solution or by a short infusion (20-30 minutes) after dilution in 125 ml of normal saline solution or dextrose 5% solution.
- The maximum tolerated dose per administration: 35.4 mg/m^2
- The maximum total dose per administration: 60 mg
- **Dose modifications:**
- Vinorelbine metabolism and clearance are mostly hepatic: only 18.5% is excreted unchanged in the urine. No prospective study relating altered metabolism of the drug to its pharmacodynamic effects is available in order to establish guidelines for Vinorelbine dose reduction in patients with impaired liver or kidney function.

- Impaired hepatic function
- Doses of vinorelbine should be reduced and the drug should be administered with caution in patients with hepatic impairment. One dosage regime described in literature suggests dosing as follows: patients with total serum bilirubin concentration of 34µmol/l or less, no dosage reduction; patients with total serum bilirubin concentration of 35 – 50 µmol/l, vinorelbine dose should be reduced to 15 mg/m^2; patients with total serum bilirubin concentration exceeding 50 µmol/l, vinorelbine dose should be reduced to 7.5 mg/m^2.

- The dose limiting toxicity of Vinorelbine is mainly neutropenia. This usually occurs between day 8 and day 12 after drug administration, is short-lived, and is not cumulative. If the neutrophil count is < 2000/mm^3 and/or platelet number is < 75000/mm^3, then the treatment should be delayed until recovery. Drug administration is expected to be delayed by 1 week in about 35% of treatment courses.

- Impaired renal function
- There is no pharmacokinetic rationale for reducing Vinorelbine dose in patients with impaired kidney function.

- Elderly:
- Studies of patients aged above 65 have not shown any significant differences in efficacy or safety. Nevertheless, geriatric patients present a greater risk of myelosuppression and cardiotoxicity with the use of antineoplastic agents in general. In addition, due to the slow destruction of the haemato-encephalic barrier, effects are more frequent on the central nervous system. Use with caution.

- Children:
- The safety and efficacy of the use of vinorelbine in children has not been established.

These are consistent with the dose and dosage schedule for the reference product.

3. TOXICOLOGY

No formal data is provided under this heading and none are required for this application.

There is a non-clinical overview written by a consultant to the pharmaceutical industry. He concluded that this medicinal product is a generic of Navelbine 10mg/ml Concentrate for Solution for Infusion.

4. CLINICAL PHARMACOLOGY

This application does not require the inclusion of a bioequivalence study as it is a generic application for a parenteral drug containing the same active substance in the same concentration as the reference product.

5. EFFICACY

No new data are submitted and none are required for this type of application.

6. SAFETY

No formal safety data are presented. The adverse events that can be expected are listed in the SPC and are consistent with those for the reference product.

7. CLINICAL OVERVIEW

There is a clinical overview written by a consultant to the pharmaceutical industry. He concludes that there is no reason why the benefit/risk ratio for this medicinal product should differ to that for Navelbine 10mg/ml Concentrate for Solution for Infusion.

8. SUMMARY OF PRODUCT CHARACTERISTICS

This is consistent with the summary of product characteristics for the reference product.

9. PATIENT INFORMATION LEAFLET

This is satisfactory and consistent with that for the reference product.

10. LABELLING

This is satisfactory.

11. DISCUSSION

The data presented has shown that Vinorelbine 10mg/ml Concentrate for Solution for Infusion is a generic product of Navelbine 10mg/ml Concentrate for Solution for Infusion.

12. RECOMMENDATIONS

The efficacy and safety of the product are satisfactory for the grant of a product licence.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Vinorelbine 10mg/ml Concentrate for Solution for Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical studies were conducted. The preclinical data submitted have not revealed any evidence of potential risks to human health from treatment with Vinorelbine 10mg/ml Concentrate for Solution for Infusion beyond the already well-described effects of vinorelbine.

EFFICACY

No new or unexpected safety concerns arise from this application.

The SPC and PIL are satisfactory and consistent with that for the reference products.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with vinorelbine is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

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STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 13th December 2004
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 17th January 2005
3	Following assessment of the applications the MHRA requested further information on 27th October 2005, 28th November 2005 and 5th September 2006.
4	The applicant responded to the MHRA's requests, providing further information on 30th August 2006 and 13th April 2007.
5	The applications were determined on 13th August 2007

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Vinorelbine 10mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Vinorelbine (as tartrate) 10 mg/ml
Each 2 ml vial contains a total content of vinorelbine (as tartrate) of 10 mg.
Each 5 ml vial contains a total content of vinorelbine (as tartrate) of 50 mg.

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 excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, from colourless to pale yellow solution, free from visible particles

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- As a single agent or in combination for the first line treatment of stage 3 or 4 non-small cell lung cancer.
- Treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen.

4.2 Posology and method of administration

Strictly by intravenous injection through an infusion line. Administration by other routes is fatal.

Administration should always be followed by a normal saline infusion to flush the vein. It is extremely important to make sure that the needle is correctly inserted into the vein before commencing the injection (see 4.4)

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- Doses of vinorelbine should be reduced and the drug should be administered with caution in patients with hepatic impairment. One dosage regime described in literature suggests dosing as follows: patients with total serum bilirubin concentration of 34µmol/l or less, no dosage reduction; patients with total serum bilirubin concentration of 35 – 50 µmol/l, vinorelbine dose should be reduced to 15 mg/m^2; patients with total serum bilirubin concentration exceeding 50 µmol/l, vinorelbine dose should be reduced to 7.5 mg/m^2.

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the neutrophil count is < 2000/mm^3 and/or platelet number is < 75000/mm^3, then the treatment should be delayed until recovery. Drug administration is expected to be delayed by 1 week in about 35% of treatment courses.

- Impaired renal function
- There is no pharmacokinetic rationale for reducing Vinorelbine dose in patients with impaired kidney function.

- Elderly:
- Studies of patients aged above 65 have not shown any significant differences in efficacy or safety. Nevertheless, geriatric patients present a greater risk of myelosuppression and cardiotoxicity with the use of antineoplastic agents in general. In addition, due to the slow destruction of the haemato-encephalic barrier, effects are more frequent on the central nervous system. Use with caution.

- Children:
- The safety and efficacy of the use of vinorelbine in children has not been established.

4.3 Contraindications

Pregnancy
Lactation
Severe hepatic impairment not related to the tumoural process
Known hypersensitivity to vinorelbine or other vinca alkaloids, or to any of the constituents
Neutrophil count <2000/mm^3 or severe current or recent infection (within the last 2 weeks)
Platelet count less than 75.000/mm^3

4.4 Special warnings and precautions for use

Vinorelbine must only be administered by the intravenous route. Administration by other routes is fatal. Administration should always be followed by a normal saline infusion to flush the vein.

It is extremely important to make sure that the needle is correctly inserted into the vein before commencing the injection. In the event of extravasation, cellulitis or even necrosis could occur. The injection should be immediately stopped and the maximum amount of product extravasated should be removed; the remaining amount should be administered into another vein.

Vinorelbine may only be used under the strict control of a doctor specialising in the use of oncological chemotherapeutics, preferably in institutions in which the staff have experience of such therapies.

Treatment should be undertaken with close haematological monitoring (determination of hemoglobin level and number of leucocytes, granulocytes and platelets before each new injection); if the neutrophil count is <2000/mm^3, 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.

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

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.

Neurological examinations must be carried out in long term treatment with vinorelbine and in patients at a high risk, such as those with pre-existing neuropathy.

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

Vinorelbine should not be given concomitantly with radiotherapy if the treatment field includes the liver. No irradiation of the pelvis, the spine or the hollow bones should be carried out simultaneously with the administration of vinorelbine, as elevated myelotoxicity can be expected in this case. The same applies to previous radiation treatment (<3 weeks) of the same regions.

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.

Contraceptive measures must be taken by both men and women during treatment and for three months after treatment has been discontinued.

4.5 Interaction with other medicinal products and other forms of interaction

The combination Vinorelbine-Cisplatin shows no interaction on the pharmacokinetic parameters. However, a higher incidence of grade 3 and 4 granulocytopenia has been reported in patients receiving combination therapy with vinorelbine and cisplatin than in those receiving vinorelbine alone.

Concomitant use of vinca alkaloids and mitomycin C increases the risk of bronchospasm and dyspnoea. In rare cases, particularly in combination with mitomycin, an interstitial pneumonitis has been observed.

The combination of vinorelbine and gemcitabine may have serious hepatic risks which can be fatal.

Vinorelbine is metabolised by CYP3A4. Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes CYP 3A4 subfamily, or other CYP3A substrates. Concomitant administration with other CYP3A4 substrates may result in increased serum levels and therefore increased toxicity of vinorelbine and other CYP3A4 substrates.

The following interactions have not been reported specifically with vinorelbine, however, they have been reported with other vinca alkaloids, and therefore caution is advised:

- phenytoin (introduced to treat the convulsive effect of certain anti-cancer drugs); risk of occurrence of convulsions through reduced digestive absorption of phenytoin by the cytostatic.
- vaccine against yellow fever; risk of generalised fatal vaccine disease.
- live vaccines; risk of generalised vaccine disease, possibly fatal. This risk is increased in subjects already immuno-depressed by the underlying disease. Use a non-living vaccine if possible.
- ciclosporin; excessive immuno-depression with risk of lympho-proliferation.
- tacrolimus; excessive immuno-depression with risk of lympho-proliferation.
- itraconazole; increase in neurotoxicity of the antimitotic by reduction of its liver metabolism.

4.6 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. Women should not become pregnant during treatment with vinorelbine. This product should not be used during pregnancy. If pregnancy should occur during the treatment, the possibility of genetic counselling should be considered.

Women of childbearing potential must be advised to use effective contraception during treatment and three months thereafter and should inform their doctor if they become pregnant.

Lactation
There are no data on the excretion of vinorelbine into breast milk. Breast-feeding must therefore be discontinued before treatment with this medicinal product.

4.7 Effects on ability to drive and use machines
Not relevant.

4.8 Undesirable effects
Grades (G) of toxicity according to WHO classification

Infections and infestations
- Infections can develop commonly, mainly due to bone marrow suppression.

Metabolism and nutrition disorders
- Rare cases of severe hyponatraemia and in very rare cases SIADH-syndrome (syndrome of inappropriate antidiuretic hormone secretion) have been reported.

Blood and 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.
- Febrile neutropenia and neutropenic sepsis which in some cases (1.2%) had a fatal outcome can occur.
- Anaemia (G1-2: 61.2%; G3-4: 7.4%) and thrombocytopenia (G1-2: 5.1%; G3-4: 2.5%) are seldom severe.

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.

Cardiac disorders
- Ischaemic heart disease (angina pectoris and/or transitory electrocardiogram modifications, myocardial infarction) has been reported in rare cases.
- As with other vinca alkaloids, vinorelbine may occasionally produce dyspnoea.

Respiratory, thoracic and mediastinal disorders
- As with other vinca alkaloids vinorelbine may incur bronchial spasms immediately after injection, or a few hours later.

There have been rare reports of interstitial lung disease, especially in patients who are given a combination of vinorelbine and mitomycin. There is a single case in which after previous radiation treatment acute respiratory failure, with a fatal outcome was observed, while vinorelbine was being administered

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.
- Anorexia is observed very commonly (G1-2: 14%; G3: 1%).
- Rare cases of pancreatitis have been reported.

Hepatobiliary disorders
- Temporary elevation of liver parameters without clinical symptoms has been reported: total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase.

Skin and subcutaneous tissue disorders
- Alopecia is mild and may appear progressively with extended courses of treatment (G1-2: 21%; G3-4: 4.1%).

Musculoskeletal, connective tissue and bone disorders
- Arthralgia including jaw pain and myalgia have been reported in patients being treated with vinorelbine.

Renal and urinary disorders
- Increased blood creatinine was observed commonly.

General disorders and administration site conditions
- Allergic type reactions have been reported.
- Reactions at the injection site can include erythema, smarting pains, discoloration of the vein and local phlebitis (G1: 12.3%; G2: 8.2%, G3: 3.6%; G4: 0.1% in monotherapy).
- As other vinca alkaloids vinorelbine has vesicant power. In rare cases local necrosis due to extravasation has been observed. This undesirable effect can be limited by correct positioning of the intravenous cannula or catheter and bolus injection, followed by liberal flushing of the vein.
- Patients being treated with vinorelbine can have fatigue, asthenia, fever and pain in different locations such as chest pain and pain in the tumor.

4.9 Overdose

Studies of acute toxicity in animals:
The symptoms of overdosage are pilo erection, behaviour abnormalities (lethargy, prostration), pulmonary lesions, weight loss and bone marrow hypoplasia more or less severe in animals sacrified during the course of the study.

Accidental overdosages have been reported in humans: they may produce a period of bone marrow aplasia sometimes associated with fever, infection and possibly paralytic ileus. Management of the infectious complications is by broad-spectrum antibiotic therapy and the paralytic ileus is managed by naso-gastric aspiration.

As no known specific antidote is known, symptomatic measures are required in every overdose. These measures include:
- Continuous checks of vital signs and especially careful monitoring of the patient.
- Daily blood count in order to detect the need for transfusion, and to estimate the infection risk and the need for intensive medical care.
- Monitoring of the cardiovascular system
- Checks on liver function.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group (ATC code) – L01C A04

Vinorelbine is a cytostatic antineoplastic drug of the vinca alkaloid family with a molecular action on the dynamic equilibrium of tubulin in the microtubular apparatus of the cell. It 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

After intravenous administration of Vinorelbine 30mg/m^2 in patients, the plasma concentration of the active ingredient is characterised by a three exponential elimination curve. The end-

elimination phase reflects a long half-life greater than 40 hours. Total clearance of vinorelbine is high (1.3 1/h/kg) with excretion occurring mainly by the biliary route; renal excretion is minimal (18.5% of label is recovered in urine).

The active ingredient is widely distributed in the body with a volume of distribution greater than 40 1/kg. There is moderate binding to plasma proteins (13.5%), but strong binding to platelets (78%). Penetration of vinorelbine into pulmonary tissue is significant with tissue/plasma concentration ratios of greater than 300 in a study involving surgical biopsy. There is moderate binding to plasma proteins (13.5 %) but strong binding to platelets (78%). Linear pharmacokinetics have been shown for intravenously administered vinorelbine up to a dose of 45 mg/m^2.

Vinorelbine is primarily metabolised by CYP3A4 of cytochrome P450. All metabolites have been identified and none are active with the exception of 4-O-deacetylvinorelbine, which is the principal metabolite in the blood.

Renal elimination is low (<20% of the dose). Small concentrations of deacetyl vinorelbine have been recovered in humans, but vinorelbine is principally detected as the unchanged compound in urine. Elimination of the active substance is mainly via the bile duct and consists of the metabolites and mainly of unchanged vinorelbine.

5.3 Preclinical safety data

Mutagenic and carcinogenic potential

The interaction of Vinorelbine with the spindle apparatus during mitosis can cause an incorrect distribution of chromosomes. In animal studies Vinorelbine induced aneuploidy and polyploidy. It is therefore to be assumed that Vinorelbine can also cause mutagenic effects (induction of aneuploidy) in man.

The carcinogenicity studies, in which Vinorelbine was administered only once every two weeks in order to avoid the toxic effects of the drug, are negative.

Reproductive toxicity

In animal reproductive studies Vinorelbine was embryo- and feto-lethal and teratogenic. The NOEL in the rat was 0.26 mg/kg every 3 days.

Following peri/postnatal administration in the rat at doses of 1.0 mg/kg every 3 days i.v., retarded weight gain was found in the offspring up to the 7th week of life.

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.

Haemodynamic and electrocardiographic studies on animals have been carried out by Pierre Fabre Medicament Laboratories; no haemodynamic effects have been found using a maximal tolerated dose in dogs, however only some non significant disturbances of depolarisation were found for all vinca alkaloids tested. No effect on the cardiovascular system has been detected using repeated doses (study 39 weeks) of Vinorelbine on primates.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

6.2 Incompatibilities

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

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

Vinorelbine is not absorbed to or affected by either PVC or clear neutral glass.

6.3 Shelf life

3 years.

Chemical and physical in use stability has been demonstrated for 48 hours at 2-8°C and at 30±2°C in PVC infusion bags and for 24 hours at 25±2°C in glass vial.

From a microbiological point of view, however, 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 when stored at 2-8°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). Keep the vial in the outer carton in order to protect from light. Do not freeze.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

The drug is distributed in glass vials (type I) of appropriated volume closed by a chlorobutyl stopper. The stopper is covered with a crimped-on aluminium cap equipped with a polypropylene seal. Vials of 2 and 5 ml.

6.6 Special precautions for disposal

Single use only.

Vinorelbine has a more or less yellow colouration, which does not affect the quality of the product.

Handling guidelines: the preparation and administration of Vinorelbine 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.

Suitable eye protection, disposable gloves, face mask and disposable apron should be worn.

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

Eventual spillage or leakage should be mopped up wearing protective gloves.

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.

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

Vinorelbine may be administered by slow bolus (5-10 minutes) after dilution in 20-50 ml of normal saline solution or by a short infusion (20-30 minutes) after dilution in 125 ml of normal saline solution. Administration should always be followed by a normal saline infusion to flush the vein.

Vinorelbine must be given strictly intravenously: it is very important to make sure that the cannule is accurately placed in the vein before starting to infuse Vinorelbine.

If the drug extravasates during intravenous administration, a substantial local reaction may occur. In this case, the injection should be stopped and the rest of the dose should be administered in another vein.

Disposal guidelines all sharps should be placed in an appropriate container and all other disposable items and cleaning materials in a sealed plastic bag which should be incinerated with other clinical waste.

Waste material may be disposed of by incineration.

7 MARKETING AUTHORISATION HOLDER

Teva UK Limited
Brampton Road; Hampden Park
Eastbourne; Sussex BN22 9JG
UNITED KINGDOM

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/0808

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/08/2007

10 DATE OF REVISION OF THE TEXT

13/08/2007

PACKAGE LEAFLET: INFORMATION FOR THE USER

Vinorelbine 10 mg/ml concentrate for solution for infusion
Vinorelbine (as tartrate)

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist

In this leaflet:

1. WHAT VINORELBINE IS AND WHAT IT IS USED FOR

The active ingredient of your medicine is Vinorelbine tartrate. It is available as a concentrate, which should be diluted before infusion and comes in two sizes:

- Each 2 ml vial contains a total of 10 mg vinorelbine (as tartrate)
- Each 5 ml vial contains a total of 50 mg vinorlebine (as tartrate)

Vinorelbine is intended for the treatment of cancer, specifically advanced non small cell lung cancer and advanced breast cancer.

If you need any further information on your condition, please ask your doctor

2. BEFORE YOU TAKE VINORELBINE

You will not be given Vinorelbine

- If you are known to be sensitive to Vinorelbine or to one of its constituents, or to other medicines belonging to the same family.
- if you are pregnant
- if you are breast-feeding
- if you have severe liver disease, which is not caused by the cancer being treated with Vinorelbine (a reduced dose may be given in some cases).

Your doctor will take special care when givig you Vinorelbine

- if you have liver problem
- if you are also receiving radiotherapy in the area of your liver
- if you show signs of infection

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
Vinorelbine should not be given to you if you are pregnant, because it can cause serious birth defects. Female patients should also avoid getting pregnant while being treated with vinorelbine and for at least three months afterwards. Male patients receiving vinorelbine should take adequate precautions to ensure that their partner does not become pregnant for the same period. If you are considering becoming parents after the treatment, you should discuss this with your doctor.

Vinorelbine should not be given to you if you are breast-feeding, as vinorelbine might pass into breast milk and affect the baby.

Driving and using machines
Vinorelbine treatment should not affect your ability to drive, but if you feel unwell, you should not drive or operate machinery.

3. HOW TO TAKE VINORELBINE

Vinorelbine is a powerful drug and your doctor will want to do a number of tests on you before you start your treatment. These will continue during the course of your treatment and will include blood tests to monitor certain critical values. If these are not satisfactory your treatment may be delayed until these values return to normal.
If you display symptoms of an infection (fever, chills, joint pain) you should let your doctor know immediately, so that further tests can be carried out.

The preparation and administration of your medicine must only be carried out by a trained healthcare professional in hospital:

- Diluted in 20 – 50 ml of saline solution and given as a slow injection into a vein over 5 – 10 minutes

or

- Diluted in 125 ml of saline solution and given as a slow drip into a vein over 20 – 30 minutes.

The dose will depend on your medical condition, whether other drugs are to be given at the same time and on a measure of your body size. After receiving your injection the vein will be rinsed through with saline solution.

If you have more Vinorelbine than you should

As a doctor or nurse will be giving you your medicine, it is unlikely that you will receive an overdose. However, if you have any concerns you should let your doctor or nurse know immediately.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Vinorelbine may have side effects.

A few people may develop an allergic reaction. This is an uncommon but very serious side effect. If you experience any of the following symptoms you should tell your doctor immediately:

- Swelling of the lips, face and neck leading to severe difficulty in swallowing or breathing.

The most frequent side effects are:

- Decrease in blood cell counts leading to tiredness, lethargy and increased risk of infections.
- Feeling sick and being sick (these symptoms usually disappear a short time after treatment)
- Constipation
- Suppression of some reflex reactions, occasionally altered touch sensations
- Moderate hair loss after long term treatment
- Jaw pain.
- A burning feeling and inflammation at the site of injection may occur after repeated treatment

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE VINORELBINE

Keep out of the reach and sight of children.
Store in a refrigerator (2-8°C). Keep the vial in the outer carton in order to protect from light. Do not freeze.
Do not use Vinorelbine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.
After dilution, chemical and physical stability has been demonstrated for 48 hours at 2-8°C and at 30±2°C in PVC infusion bags and for 24 hours at 25±2°C in glass vial
From a microbiological point of view, the infusion preparation 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. FURTHER INFORMATION

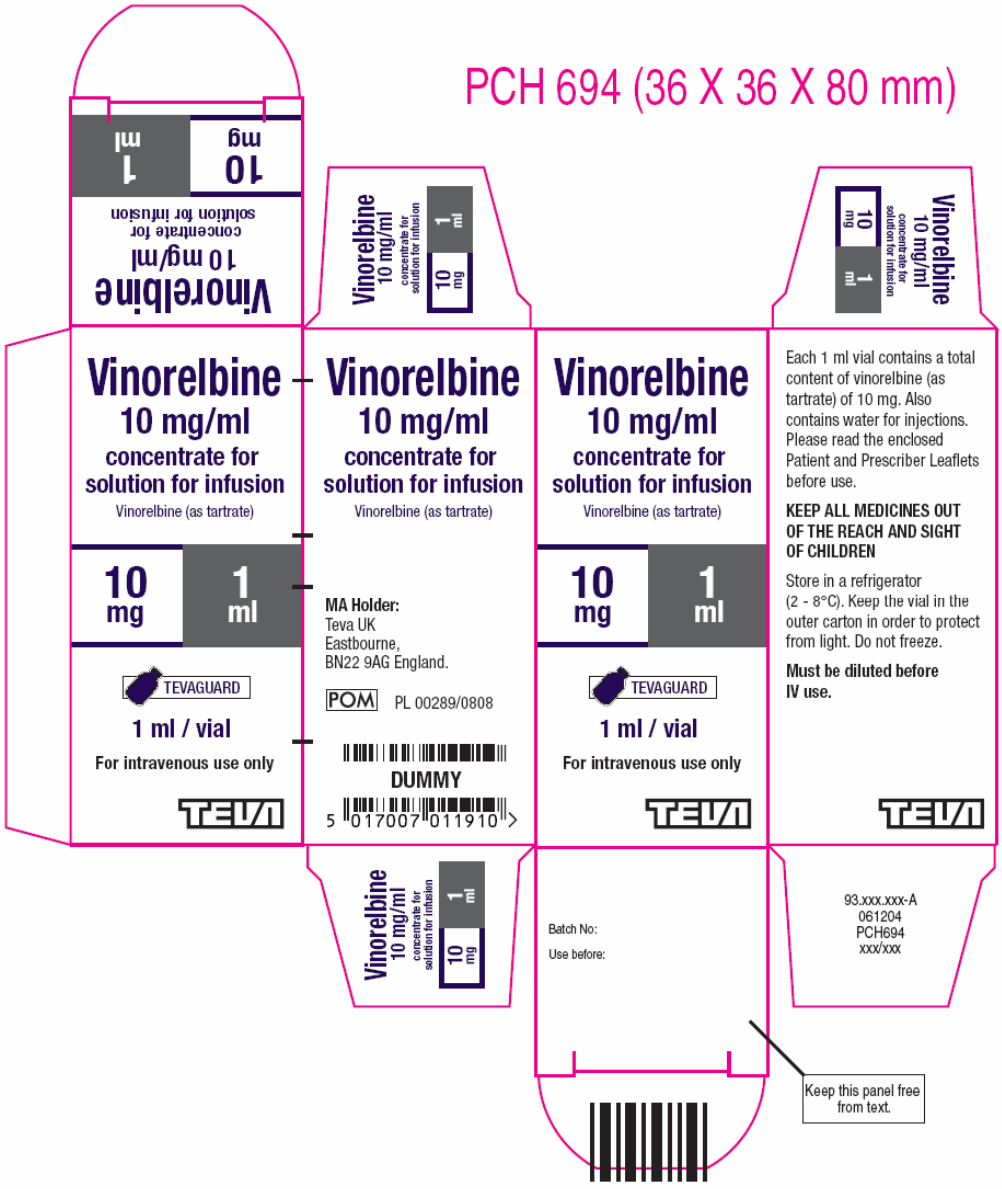
What Vinorelbine contains
- The active substance is: Vinorelbine (as tartrate)
- The other ingredient is: Water for injection

What Vinorelbine looks like and contents of the pack
Vinorelbine concentrate is a clear, from colourless to pale yellow liquid.

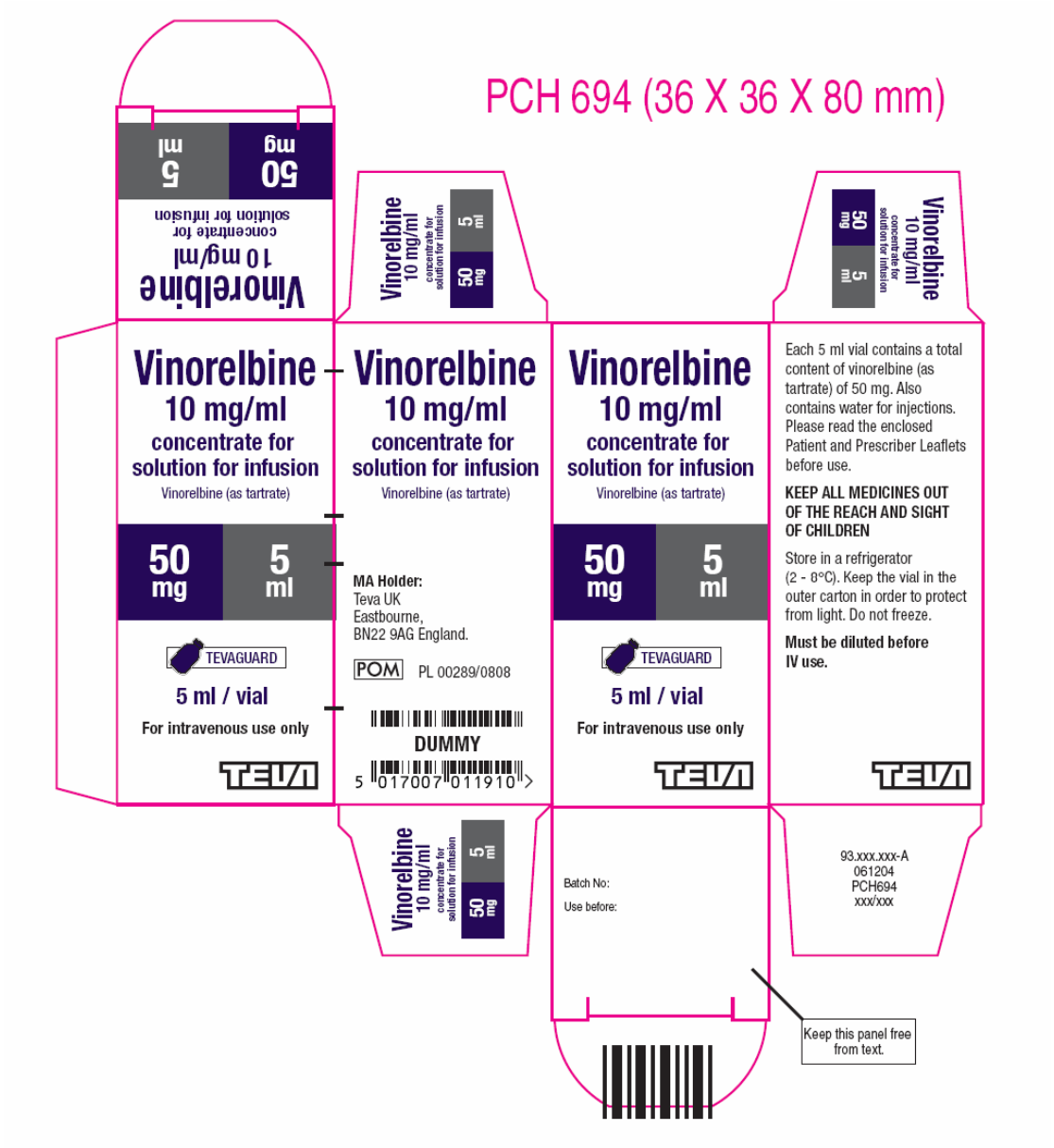
Marketing Authorisation Holder and Manufacturer
The Marketing Authorisation holder is Teva UK Limited, Eastbourne BN22 9AG England.
The company responsible for manufacture is: Pharmachemie B.V., Haarlem, The Netherlands

Revised: March 2007

PCH 694 (36 X 36 X 80 mm)




Vinorelbine 10 mg/ml
concentrate for solution for infusion
Vinorelbine (as tartrate)
50 mg
5 ml
For intravenous use only.
5 ml / vial
Must be diluted before IV use.
Teva UK
Eastbourne,
BN22 9AG England
Keep free from text
Batch:
Exp:


PCH 694 (36 X 36 X 80 mm)
Vinorelbine
10 mg/ml
concentrate for solution for infusion
Vinorelbine (as tartrate)
50 mg
5 ml
TEVAGUARD
5 ml / vial
For intravenous use only
MA Holder:
Teva UK
Eastbourne,
BN22 9AG England.
POM
PL 00289/0808
DUMMY
5 017007 011910
Each 5 ml vial contains a total content of vinorelbine (as tartrate) of 50 mg. Also contains water for injections. Please read the enclosed Patient and Prescriber Leaflets before use.
KEEP ALL MEDICINES OUT OF THE REACH AND SIGHT OF CHILDREN
Store in a refrigerator (2 - 8°C). Keep the vial in the outer carton in order to protect from light. Do not freeze.
Must be diluted before IV use.
Batch No:
Use before:
93.xxx.xxx-A
061204
PCH694
xxx/xxx
Keep this panel free from text.