Safeguarding public health

MHRA

Public Assessment Report

Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion

PL 04543/0500
PL 04543/0501

Medicines and Healthcare products Regulatory Agency

VINORELBINE 10MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

PL 04543/0500
PL 04543/0501

UKPAR

TABLE OF CONTENTS

	Page
Lay Summary	3
Scientific discussion	4
Steps taken for assessment	15
Steps taken after authorisation – summary	16
Summary of Product Characteristics	17
Patient Information Leaflet	35
Labelling	39

VINORELBINE 10MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

PL 04543/0500
PL 04543/0501

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted CP Pharmaceuticals Limited Marketing Authorisations (licences) for the medicinal product Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion (PL 04543/0500 [1ml]; PL 04543/0501 [5ml]). This is a prescription only medicine [POM] used to treat certain types of lung and breast cancer.

This product contains the active substance vinorelbine tartrate, which belongs to a group of anticancer medicines known as cytotoxics.

The clinical data presented to the MHRA, before licensing, demonstrated that Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion is essentially similar or equivalent to the approved product, Navelbine 10mg/ml Concentrate for solution for infusion, and as such can be used interchangeably.

No new or unexpected safety concerns arose from these applications and it was decided that the benefits of using Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion outweigh the risks, hence Marketing Authorisations have been granted.

VINORELBINE 10MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

PL 04543/0500
PL 04543/0501

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

	Page
Introduction	5
Pharmaceutical assessment	6
Preclinical assessment	11
Clinical assessment	12
Overall conclusions and risk benefit assessment	14

INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal product Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion (PL 04543/0500 [1ml]; PL 04543/0501 [5ml]) to CP Pharmaceuticals Limited on 22 June 2006. Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion is a prescription only medicine.

The applications were submitted as abridged applications according to Article 10.1(a)(iii) of Directive 2001/83/EC, claiming essential similarity to Navelbine 10mg/ml, which was first authorised in France on 11 April 1989.

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

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.

PHARMACEUTICAL ASSESSMENT

LICENCE No.:	**PLs 04543/0500-1**
PROPRIETARY NAME:	**Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion**
ACTIVE:	**Vinorelbine tartrate**
COMPANY NAME:	**CP Pharmaceuticals Ltd**
EC ARTICLE:	**10.1(a)iii**
LEGAL STATUS:	**POM**

INTRODUCTION

These are abridged applications for Marketing Authorisations in the UK that were submitted under Article 10.1(a)(iii), first paragraph of Directive 2001/83/EC, the so-called generic application.

The original product, Navelbine 10mg/ml, was first licensed in France on 11 April 1989. The reference product is listed as Navelbine 10mg/ml licensed in the UK on 10 May 1996 to Pierre Fabre Limited (PL 00603/0028). Documentation has been supplied demonstrating registration of the product in France since 1989.

DRUG SUBSTANCE

General information

Description:	White to almost white powder which is hygroscopic. Freely soluble in water and alcohol; practically insoluble in hexane.
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 3',4'-Didehydro-4'-deoxy-8'-norvincaleukoblastine ditartrate
Molecular formula:	$C_{45}H_{54}N_4O_8 \cdot 2(C_4H_6)_6$
Relative mol. mass:	1079.11

Control of active substance

Specification

Vinorelbine tartrate has a European Pharmacopoeia monograph.

The finished product manufacturer specification is in compliance with the requirements of the European Pharmacopoeia.

The limits included for the residual solvents are in compliance with the relevant guidelines.

Analytical test methods

Relevant details have been provided on the pharmacopoeial and non-pharmacopoeial methods.

Analytical test method validation

No validation data has been presented for the pharmacopoeial methods, which is acceptable. The assay method is that used for the finished product.

Reference standards

Relevant information on the reference standards has been supplied.

DRUG PRODUCT

Composition

The products are solutions for injection and infusion. The products are a concentrate at a concentration of 10mg/ml, with the only difference being the fill volume.

The products are packed in colourless Type I glass vials according to the European Pharmacopoeia and dimensions according to DIN ISO 8362, parts 1 and 4. The vials have a fluoropolymer-coated rubber stopper with a metal cap. The composition is shown below.

Product composition

Ingredients	Function	Quality reference
Vinorelbine tartrate	Active	-
Water for injections	Solvent	Ph.Eur.
Nitrogen	Inert gas	Ph.Eur.

Manufacture

Manufacturer(s)

Batch release site: Ebewe Pharma Ges.m.b.H. Nfg.KG, Mondseestrasse 11, 4866 Unterach, Austria.

Batch formula

The batch formula for two batch sizes has been presented.

In addition to the components of the formulation, nitrogen is listed and is used as a pressure medium during filtration.

Manufacturing process and process controls

A flow diagram detailing the manufacturing process and in-process control testing has been provided.

Control of excipients

Specification

Water for injections and nitrogen both have monographs in the European Pharmacopoeia. Batch analysis from one batch of each excipient has been provided, which are in compliance with the monograph.

The analytical methods used to test the excipients are those provided in the European Pharmacopoeia. Consequently no validation data has been supplied.

No excipients of human or animal origin have been used in the manufacture of the finished product.

Control of drug product

Specification

A satisfactory finished product specification has been provided.

Analytical procedures

All the details have been provided for the pharmacopoeial and non-pharmacopoeial methods.

Validation

Suitable validation data have been provided, where appropriate.

Reference standards

Suitable information on the reference standards has been provided.

Batch analysis

Batch analysis has been provided for batches of the two fill volumes. These are the batches used in the validation.

The specifications are satisfied for all of the batches, which are all very comparable. The related impurity values are low in relation to the specification and all comply with the requirements for sterility and bacterial endotoxins.

Characterisation of impurities

Certificates of Analysis have been supplied for the known impurities.

Container closure system

The injection vials are Type I, colourless, moulded glass and comply with the requirements of the European Pharmacopoeia, with a nominal capacity of 1ml and 5ml.

The closures are grey fluoropolymer coated rubber stoppers. These comply with the requirements of the European Pharmacopoeia.

The metallic cap is aluminium sheet. This item is not in contact with the finished product.

Relevant specifications and routine tests have been supplied from the finished product manufacturer, which are acceptable. Drawings have also been supplied.

Stability

Stability has been determined for the validation batches which were split and filled into both the 1ml and 5ml presentations. These contain various batches of the active substance. All batches have been stored at 2°C to 8°C, 25°C/60%RH and 40°C/75%RH.

Photostability testing clearly demonstrates the requirement to protect the product from light.

Sodium chloride solution 0.9% and glucose 5% have been demonstrated to be suitable infusion fluids.

The applicant is proposing a shelf life of 36 months when stored between 2°C to 8°C and "Keep the vial in the outer carton". This is acceptable on the basis of the data presented.

After first opening or following reconstitution the applicant has recommended that the product should be used as soon as possible in line with the guidelines. The following standard statement has been included "From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions."

A suitable stability commitment has been supplied by the applicant.

OTHER INFORMATION

Biostudy

No new clinical work has been presented on the basis that the product is well known.

Essential similarity

Comparable impurity profiles and levels have been demonstrated for one batch of the finished product and three batches of the reference product (Navelbine).

PRODUCT LITERATURE

Satisfactory.

ADMINISTRATIVE

Quality Overall Summary

The report is an acceptable summary of the module.

CONCLUSION

Marketing authorisations can be granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required.

CLINICAL ASSESSMENT

LICENCE No.:	**PLs 04543/0500-1**
PROPRIETARY NAME:	**Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion**
ACTIVE:	**Vinorelbine tartrate**
COMPANY NAME:	**CP Pharmaceuticals Ltd**
EC ARTICLE:	**10.1(a)iii**
LEGAL STATUS:	**POM**

INTRODUCTION

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.

These applications consider an essentially similar product to Navelbine 10 mg/ml Concentrate for solution for infusion. The applicant has submitted two applications PL 04543/0500 for a vial size of 10mg in 1ml and PL 04543/0501 for a vial size of 50mg in 5ml.

BACKGROUND

Pierre Fabre was granted a product licence in the UK (PL 00603/0028) for Navelbine, 10 mg/ml Concentrate for solution for infusion on 10 May 1996. The applicant states that the date of first authorisation for Navelbine in the EU was 11 April 1989 (France); thus the 10-year rule has been fulfilled.

INDICATIONS

The indications in Section 4.1 of the Summary of Product Characteristics (SPC) are consistent with those of Navelbine.

DOSE AND DOSE SCHEDULE

Section 4.2 of the SPC is consistent with that of Navelbine.

TOXICOLOGY

No formal data provided under this heading and none are required for these applications.

The Non-Clinical Overview concludes that this medicinal product is essentially similar to Navelbine.

CLINICAL PHARMACOLOGY

These applications do not require the inclusion of a bioequivalence study as the applications are claiming essential similarity for a parenteral drug containing the same active substance in the same concentration as the reference product.

EFFICACY

No new data are submitted and none are required for these applications.

SAFETY

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

CLINICAL OVERVIEW

The Clinical Overview concludes that there is no reason why the benefit/risk ratio for this medicinal product should differ from that of Navelbine.

SPC

The SPC is entirely consistent with that of the innovator product Navelbine.

PATIENT INFORMATION LEAFLET
LABELLING

Satisfactory.

DISCUSSION

The data presented has shown that Vinorelbine 10mg/ml Concentrate for solution for injection or infusion is essentially similar to Navelbine 10mg/ml Concentrate for solution for infusion.

RECOMMENDATION

The efficacy and safety of the product are satisfactory for the grant of marketing authorisations.

OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Vinorelbine 10mg/ml Concentrate for Solution for Injection or 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 data were submitted and none are required for applications of this type.

EFFICACY

No clinical pharmacology data or clinical trials data have been submitted to directly support the claim of essential similarity of the proposed product to the proprietary product Navelbine 10mg/ml Concentrate for Solution for Infusion (PL 00603/0028). This is acceptable as the formulations are similar and the same routes of administration are proposed.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those of Navelbine 10mg/ml Concentrate for Solution for Infusion.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The risk-benefit assessment is therefore considered to be favourable.

VINORELBINE 10MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

PL 04543/0500
PL 04543/0501

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation applications for Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion 1ml and 5ml on 4 June 2004.
2	The MHRA's assessment of the submitted clinical data was completed on 21 February 2005.
3	Further information (clinical) was requested from the company on 22 February 2005.
4	The applicant's response to further information (clinical) request was received on 1 March 2005.
5	The MHRA's assessment of the submitted quality data was completed on 30 March 2005.
6	Further information (quality) was requested from the company in a letter dated 26 May 2005.
7	The applicant's response to further information request (quality) was sent in a letter dated 19 January 2006.
8	Further information (quality) was requested from the company in a letter dated 20 March 2006.
9	The applicant's response to further information request (quality) was received on 6 June 2006.
10	The MHRA completed its assessment of the application on 22 June 2006.
11	The application was determined on 22 June 2006.

VINORELBINE 10MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

PL 04543/0500
PL 04543/0501

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 Injection or Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vinorelbine (as tartrate) 10mg/ml

Each 1ml vial contains a total content of vinorelbine (as tartrate) of 10mg

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Concentrate for solution for injection or infusion
A clear, colourless to pale yellow solution

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.

The use of intrathecal route is contra-indicated.

Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion may be diluted in a solution for infusion of normal saline or 5% dextrose.

The volume of dilution depends on the mode of administration:

bolus = 20-50 ml

infusion = 125 ml

In adults:

Vinorelbine Concentrate for Solution for Injection or Infusion is usually given at 25-30mg/m² weekly.

Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion may be administered by slow bolus (five to ten minutes) after dilution in 20-50ml of normal saline solution or by a short infusion (20-30 minutes) after dilution in 125ml of normal saline solution. Administration should always be followed by a normal saline infusion to flush the vein.

Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion must be given strictly intravenously; it is very important to make sure that the cannula is accurately placed in the vein before starting to infuse Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion.

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.

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.

However, in breast cancer patients, vinorelbine clearance is not altered in presence of moderate liver metastases (i.e. □ 75% of liver volume replaced by the tumour). In these patients, there is no pharmacokinetic rationale for reducing vinorelbine doses.

In patients with massive liver metastases (i.e. > 75% of liver volume replaced by the tumour), it is empirically suggested that the dose be reduced by ⅓ and the haematological toxicity closely followed-up.

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

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 one week in about 35% of treatment courses.

<u>The maximum tolerated dose per administration</u>: 35.4mg/m²

<u>The maximum total dose per administration</u>: 60 mg

4.3. Contraindications

Pregnancy
Lactation
Severe hepatic insufficiency not related to the tumoural process.

4.4. Special warnings and precautions for use

Vinorelbine Concentrate for Solution for Injection or Infusion must only be administered by the intravenous route. The use of intrathecal route is contraindicated. Administration should always be followed by a normal saline infusion to flush the vein.

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

If there is significant hepatic impairment the dose should be reduced.

In case of renal impairment, because of the low level of renal excretion, no dose modification is necessary.

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

All contact with the eye should be strictly avoided: risk of severe irritation and even corneal ulceration if the drug is sprayed under pressure. Immediate liberal washing of the eye with normal saline solution should be undertaken if any contact occurs.

4.5. Interactions with other medicinal products and other forms of interaction

The combination vinorelbine-cisplatin shows no interaction on the pharmacokinetic parameters.

4.6. Pregnancy and lactation

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

Women should not become pregnant during treatment with vinorelbine.

This product should not be used during pregnancy.

If pregnancy should occur during treatment, the possibility of genetic counselling should be used.

It is not known whether vinorelbine passes into the breast milk. Lactation must therefore be discontinued before treatment with this medicine

4.7. Effects on ability to drive and use machines

Not applicable.

4.8. Undesirable effects

Haematological tolerance

The limiting toxicity is neutropenia (Grade1: 9.7%; Grade 2 : 15.2%; Grade 3 : 24.3%; Grade 4: 27.8%) which is rapidly reversible (five to seven days) and non-cumulative; it is maximal between five and seven days after administration. Further treatment may be given after recovery of the granulocyte count.

Anaemia (Grade1-2: 61.2%; Grade 3-4: 7.4%) and thrombocytopenia (Grade 1-2: 5.1%; Grade 3-4: 2.5%) are seldom severe.
Neurological tolerance

Peripheral

This is generally limited to loss of deep tendon reflexes; severe paraesthesiae are uncommon (Grade1: 17.2%; Grade 2: 3.6%; Grade 3 : 2.6%; Grade 4 : 0.1%). The effects are dose dependent but reversible when treatment is discontinued.

Autonomic neuropathy

The main symptom is intestinal paresis causing constipation (Grade 1: 16.9%; Grade 2: 4.9%) which rarely progresses to paralytic ileus (Grade 3: 2%; Grade 4: 0.7%). Treatment may be resumed after recovery of normal bowel mobility.

Gastrointestinal tolerance

Constipation (see autonomic neuropathy)

Diarrhoea (Grade 1: 7.6%; Grade 2: 3.6%; Grade 3: 0.7%; Grade 4: 0.1%): severe diarrhoea is uncommon.

Nausea-vomiting (Grade 1: 19.9%; Grade 2: 8.3%; Grade 3: 1.9%; Grade 4 : 0.3%): severe nausea and vomiting may occasionally occur. Conventional anti-emetic therapy reduces these undesirable effects.

Allergic reactions

As with other vinca alkaloids, vinorelbine may occasionally produce dyspnoea and bronchospasm and more rarely local or generalised cutaneous reactions.

Venous tolerance

Burning pain at the injection site and local phlebitis (Grade 1: 12.3%; Grade 2: 8.2%; Grade 3 : 3.6%; Grade 4 : 0.1%) may be observed with repeated injections of vinorelbine.

Bolus injection followed by liberal flushing of the vein can limit this effect. Insertion of a central venous line may be necessary.

Other undesirable effects

Alopecia is mild and may appear progressively with extended courses of treatment (Grade 1-2 : 21%; Grade 3-4 : 4.1%)

Jaw pain has occasionally been reported.

Any extravasation may induce local reactions, which rarely progress to necrosis (see 4.2. Posology and method of administration).

4.9. Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC code: LO 1 CA04
Group: Antineoplastic agents, plant alkaloids and other natural products

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/m² in patients, the plasma concentration of the active ingredient is characterised by a three phase exponential elimination curve. The end-elimination phase reflects a long half-life greater than 40 hours. Total clearance of vinorelbine is high (1.3 l/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 l/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.

Small concentrations of deacetyl vinorelbine have been recovered in humans, but vinorelbine is principally detected as the parent compound in urine.

5.3. Preclinical safety data

Studies of acute toxicity in animals

The symptoms of overdose are piloerection, behaviour abnormalities (lethargy, prostration), pulmonary lesions, weight loss and bone marrow hypoplasia, more or less severe, in animals sacrificed during the course of the study.

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 three days.

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

Safety pharmacology.

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

No haemodynamic effects have been found using a maximal tolerated dose in dogs, only some non significant disturbances of repolarization 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 10mg/ml Concentrate for Solution for Injection or Infusion may be diluted in a solution for infusion of normal saline or 5% dextrose.

The volume of dilution depends on the mode of administration:

Bolus = 20-50 ml

Infusion = 125 ml

Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion should not be diluted in alkaline solutions (risk of precipitate)

In case of polychemotherapy, Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion 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

36 months –unopened
After dilution, see section 6.4 Special precautions for storage.

Discard any unused solution immediately after use.

6.4. Special precautions for storage

Store in a refrigerator. Keep the vial in the outer carton.

After dilution:-
Chemical and physical in use stability has been demonstrated for 28 days at 2-8°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.

6.5. Nature and contents of container

Colourless Type I glass vial with fluropolymer-coated chlorobutyl rubber stoppers and aluminium overseal.

Packs of 1 or 10 vials containing 1ml of Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

Vinorelbine Concentrate has a pale yellow colouration which does not affect the quality of the product.

Handling guidelines: the preparation and administration of Vinorelbine Concentrate 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).

Actual 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.

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

CP Pharmaceuticals Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8. MARKETING AUTHORISATION NUMBER

PL 04543/0500

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/06/2006

10 DATE OF REVISION OF THE TEXT

22/06/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vinorelbine (as tartrate) 10mg/ml

Each 5ml vial contains a total content of vinorelbine (as tartrate) of 50mg

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Concentrate for solution for injection or infusion
A clear, colourless to pale yellow solution

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.

The use of intrathecal route is contra-indicated.

Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion may be diluted in a solution for infusion of normal saline or 5% dextrose.

The volume of dilution depends on the mode of administration:

bolus = 20-50 ml

infusion = 125 ml

In adults:

Vinorelbine Concentrate for Solution for Injection or Infusion is usually given at 25-30mg/m² weekly.

Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion may be administered by slow bolus (five to ten minutes) after dilution in 20-50ml of normal saline solution or by a short infusion (20-30 minutes) after dilution in 125ml of normal saline solution. Administration should always be followed by a normal saline infusion to flush the vein.

Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion must be given strictly intravenously; it is very important to make sure that the cannula is accurately placed in the vein before starting to infuse Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion.

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.

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.

However, in breast cancer patients, vinorelbine clearance is not altered in presence of moderate liver metastases (i.e. □ 75% of liver volume replaced by the tumour). In these patients, there is no pharmacokinetic rationale for reducing vinorelbine doses.

In patients with massive liver metastases (i.e. > 75% of liver volume replaced by the tumour), it is empirically suggested that the dose be reduced by ⅓ and the haematological toxicity closely followed-up.

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

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 one week in about 35% of treatment courses.

<u>The maximum tolerated dose per administration</u>: 35.4mg/m²

<u>The maximum total dose per administration</u>: 60 mg

4.3. Contraindications

Pregnancy
Lactation
Severe hepatic insufficiency not related to the tumoural process.

4.4. Special warnings and precautions for use

Vinorelbine Concentrate for Solution for Injection or Infusion must only be administered by the intravenous route. **The use of intrathecal route is contraindicated**. Administration should always be followed by a normal saline infusion to flush the vein.

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

If there is significant hepatic impairment the dose should be reduced.

In case of renal impairment, because of the low level of renal excretion, no dose modification is necessary.

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

All contact with the eye should be strictly avoided: risk of severe irritation and even corneal ulceration if the drug is sprayed under pressure. Immediate liberal washing of the eye with normal saline solution should be undertaken if any contact occurs.

4.5. Interactions with other medicinal products and other forms of interaction

The combination vinorelbine-cisplatin shows no interaction on the pharmacokinetic parameters.

4.6. Pregnancy and lactation

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

Women should not become pregnant during treatment with vinorelbine.

This product should not be used during pregnancy.

If pregnancy should occur during treatment, the possibility of genetic counselling should be used.

It is not known whether vinorelbine passes into the breast milk. Lactation must therefore be discontinued before treatment with this medicine

4.7. Effects on ability to drive and use machines

Not applicable.

4.8. Undesirable effects

Haematological tolerance

The limiting toxicity is neutropenia (Grade1: 9.7%; Grade 2 : 15.2%; Grade 3 : 24.3%; Grade 4: 27.8%) which is rapidly reversible (five to seven days) and non-cumulative; it is maximal between five and seven days after administration. Further treatment may be given after recovery of the granulocyte count.

Anaemia (Grade1-2: 61.2%; Grade 3-4: 7.4%) and thrombocytopenia (Grade 1-2: 5.1%; Grade 3-4: 2.5%) are seldom severe.
Neurological tolerance

Peripheral

This is generally limited to loss of deep tendon reflexes; severe paraesthesiae are uncommon (Grade1: 17.2%; Grade 2: 3.6%; Grade 3 : 2.6%; Grade 4 : 0.1%). The effects are dose dependent but reversible when treatment is discontinued.

Autonomic neuropathy

The main symptom is intestinal paresis causing constipation (Grade 1: 16.9%; Grade 2: 4.9%) which rarely progresses to paralytic ileus (Grade 3: 2%; Grade 4: 0.7%). Treatment may be resumed after recovery of normal bowel mobility.

Gastrointestinal tolerance

Constipation (see autonomic neuropathy)

Diarrhoea (Grade 1: 7.6%; Grade 2: 3.6%; Grade 3: 0.7%; Grade 4: 0.1%): severe diarrhoea is uncommon.

Nausea-vomiting (Grade 1: 19.9%; Grade 2: 8.3%; Grade 3: 1.9%; Grade 4 : 0.3%): severe nausea and vomiting may occasionally occur. Conventional anti-emetic therapy reduces these undesirable effects.

Allergic reactions

As with other vinca alkaloids, vinorelbine may occasionally produce dyspnoea and bronchospasm and more rarely local or generalised cutaneous reactions.

Venous tolerance

Burning pain at the injection site and local phlebitis (Grade 1: 12.3%; Grade 2: 8.2%; Grade 3 : 3.6%; Grade 4 : 0.1%) may be observed with repeated injections of vinorelbine.

Bolus injection followed by liberal flushing of the vein can limit this effect. Insertion of a central venous line may be necessary.

Other undesirable effects

Alopecia is mild and may appear progressively with extended courses of treatment (Grade 1-2 : 21%; Grade 3-4 : 4.1%)

Jaw pain has occasionally been reported.

Any extravasation may induce local reactions, which rarely progress to necrosis (see 4.2. Posology and method of administration).

4.9. Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC code: LO 1 CA04
Group: Antineoplastic agents, plant alkaloids and other natural products

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/m² in patients, the plasma concentration of the active ingredient is characterised by a three phase exponential elimination curve. The end-elimination phase reflects a long half-life greater than 40 hours. Total clearance of vinorelbine is high (1.3 l/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 l/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.

Small concentrations of deacetyl vinorelbine have been recovered in humans, but vinorelbine is principally detected as the parent compound in urine.

5.3. Preclinical safety data

Studies of acute toxicity in animals

The symptoms of overdose are piloerection, behaviour abnormalities (lethargy, prostration), pulmonary lesions, weight loss and bone marrow hypoplasia, more or less severe, in animals sacrificed during the course of the study.

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 three days.

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

Safety pharmacology.

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

No haemodynamic effects have been found using a maximal tolerated dose in dogs, only some non significant disturbances of repolarization 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 10mg/ml Concentrate for Solution for Injection or Infusion may be diluted in a solution for infusion of normal saline or 5% dextrose.

The volume of dilution depends on the mode of administration:

Bolus = 20-50 ml

Infusion = 125 ml

Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion should not be diluted in alkaline solutions (risk of precipitate)

In case of polychemotherapy, Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion 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

36 months –unopened
After dilution, see section 6.4 Special precautions for storage.

Discard any unused solution immediately after use.

6.4. Special precautions for storage

Store in a refrigerator. Keep the vial in the outer carton.

After dilution:-
Chemical and physical in use stability has been demonstrated for 28 days at 2-8°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.

6.5. Nature and contents of container

Colourless Type I glass vial with fluropolymer-coated chlorobutyl rubber stoppers and aluminium overseal.

Packs of 1 or 10 vials containing 1ml of Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

Vinorelbine Concentrate has a pale yellow colouration which does not affect the quality of the product.

Handling guidelines: the preparation and administration of Vinorelbine Concentrate 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).

Actual 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.

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

CP Pharmaceuticals Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8. MARKETING AUTHORISATION NUMBER

PL 04543/0501

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/06/2006

10 DATE OF REVISION OF THE TEXT

22/06/2006

Patient Information Leaflet

VINORELBINE 10MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

PL 04543/0500
PL 04543/0501

PACKAGE LEAFLET

Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion
Vinorelbine (as tartrate).

Read all of this leaflet carefully before you are given this medicine. Keep this leaflet. You may need to read it again. If you have further questions, please ask your doctor or nurse.

In this leaflet:

1. What is vinorelbine and what is it used for?
2. Before you are given vinorelbine
3. How vinorelbine will be given to you
4. Possible side effects
5. Storing vinorelbine

The active substance in the injection is vinorelbine (as tartrate). Each 1ml vial contains a total content of vinorelbine (as tartrate) of 10mg and each 5ml vial contains a total content of vinorelbine (as tartrate) of 50mg.

The other ingredient is water for injections.

Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion is manufactured by EBEWE Pharma Ges.m.b.H. Nfg. KG, A-4866 Unterach, Austria for the Marketing Authorisation holder CP Pharmaceuticals Ltd, Ash Road North, Wrexham LL13 9UF.

1. WHAT IS VINORELBINE CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION AND WHAT IS IT USED FOR?

Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion is a concentrated form of vinorelbine which must be diluted before use. It is available in packs of 1 or 10 vials containing 10mg of vinorelbine in 1ml of solution or 50mg of vinorelbine in 5ml of solution.

Vinorelbine 10mg/ml Concentrate for Solution for Injection or Infusion is a clear, colourless to pale yellow solution free from particles.

Vinorelbine belongs to a group of medicines known as cytotoxics, which are used in the treatment of cancer. Vinorelbine may be used to treat breast cancer and lung cancer.

2. BEFORE YOU ARE GIVEN VINORELBINE CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

You will not be given Vinorelbine Concentrate for Solution for Injection for Infusion:

- if you are allergic to vinorelbine or any of the other ingredients
- if you are pregnant, breast-feeding or trying for a baby
- if you have a severe liver disease not caused by cancer

Your doctor will take special care when giving you vinorelbine:

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

Consult your doctor if any of the above warnings applies to you or has applied to you in the past.

Your doctor will also check your blood before, during and after every treatment. If the results of any of these tests are abnormal treatment will only be resumed when all readings are back to normal.

Pregnancy

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 six 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.

Men who wish to father children in the future should seek advice about freezing sperm before the vinorelbine treatment is started.

Breast-feeding

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.

Being given vinorelbine at the same time as other medication

There should not be any problem if vinorelbine is given at the same time as other medicines. However, tell your doctor or pharmacist about medicines you are currently taking or have taken recently. This also applies to medicines you may have bought yourself from a pharmacy or supermarket.

3. HOW VINORELBINE CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION WILL BE GIVEN TO YOU

Vinorelbine Concentrate for Solution for Injection or Infusion will only be given to you under the supervision of a doctor specialised in this type of treatment.

The dosage of vinorelbine depends on the condition you are being treated for, your response to the therapy and other medication you are being given. The vinorelbine concentrate should be diluted before use with a solution of sodium chloride or dextrose and given as an injection or infusion (drip) into a vein. **IT SHOULD NOT BE INJECTED INTO THE SPINE.**

When receiving vinorelbine for treatment of lung cancer

The usual dosage of vinorelbine is 25-30mg per square metre of body surface area given by injection over 5-10 minutes or by infusion over 20-30 minutes once a week.

When receiving vinorelbine for treatment of breast cancer

The usual dosage of vinorelbine is 25-30mg per square metre of body surface area given by injection over 5-10 minutes or by infusion over 20-30 minutes once a week.

Following your treatment, a solution of sodium chloride will be used to flush the vein.

Dosage will be reduced if you have severe liver problems.

Your general condition and your response to the treatment will be closely observed before, during and after the vinorelbine treatment.

4. POSSIBLE SIDE EFFECTS

Like any other medication, vinorelbine may cause side-effects.

These include nausea, vomiting, diarrhoea, constipation, ”pins and needles”, jaw pain and temporary hair loss.

As well as killing the cancer cells, the medicine may also affect some of your own cells especially the cells in your blood. This may make you anaemic or prone to infections or to bleeding or bruising easily. If you think you have an infection, a sore throat, mouth ulcers, fever, chills or achiness you should contact your doctor.

Pain may occur temporarily at the injection site.

Allergic reactions to vinorelbine can occur, with wheezing, a skin rash or swelling of your lips, eyes or tongue. You should contact your doctor **immediately** if you develop such symptoms.

Vinorelbine can harm unborn babies (see section on pregnancy). It may also affect fertility in men and women.

If you get any vinorelbine in your eyes you should rinse with lots of water and tell your doctor or nurse immediately..

During the treatment with vinorelbine your general condition will be closely monitored.

If you notice any side-effects not mentioned in this leaflet, please tell your doctor or nurse.

5. STORING VINORELBINE

Keep out of the reach and sight of children
Store in a refrigerator. Keep the vial in the outer carton.

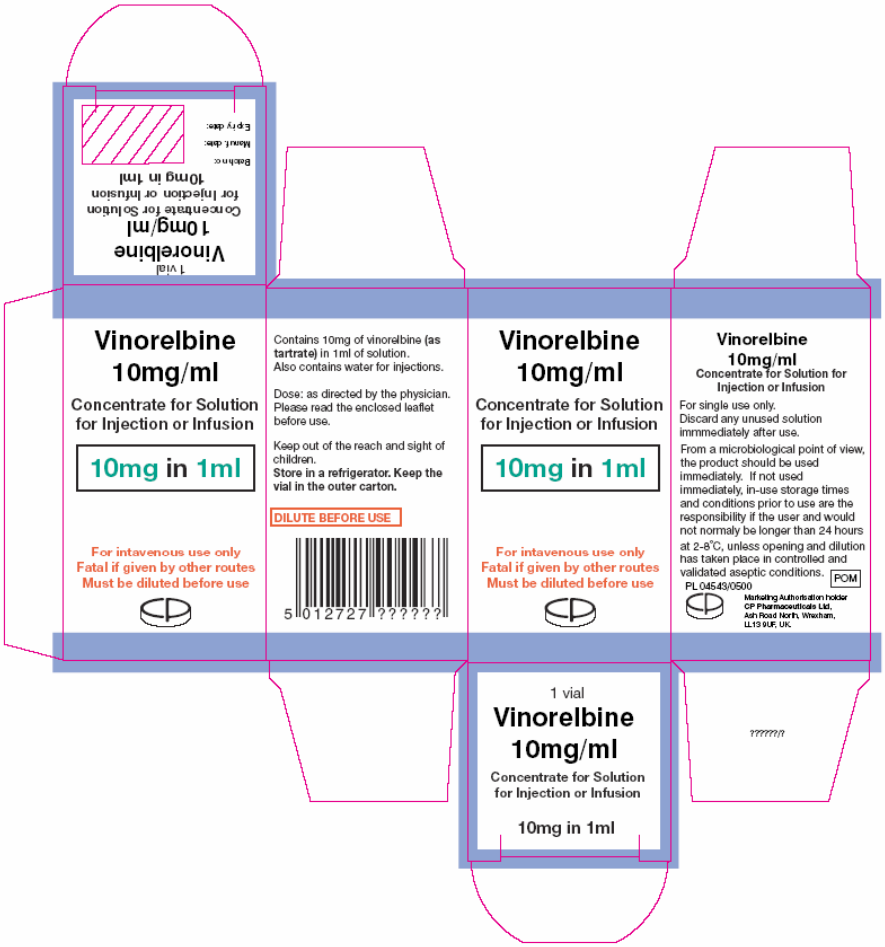
Do not use after the expiry date stated on the label.
After dilution, chemical and physical in use stability has been demonstrated for 28 days at 2-8°C.
From a microbiological point of view, the infusion preparation should be used immediately. If not used immediately, in-use storage times and conditions 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.

This leaflet was prepared in January 2006

Labels/Packaging

VINORELBINE 10MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

PL 04543/0500



VINORELBINE 10mg/ml
Concentrate for Solution for injection or Infusion
1ml vial Carton
Version 7 Mock-up 17/03/06
Colour: Pantone 2716C, 3278C, Warm Red, Black
Size: 38mm x 38mm x 70mm

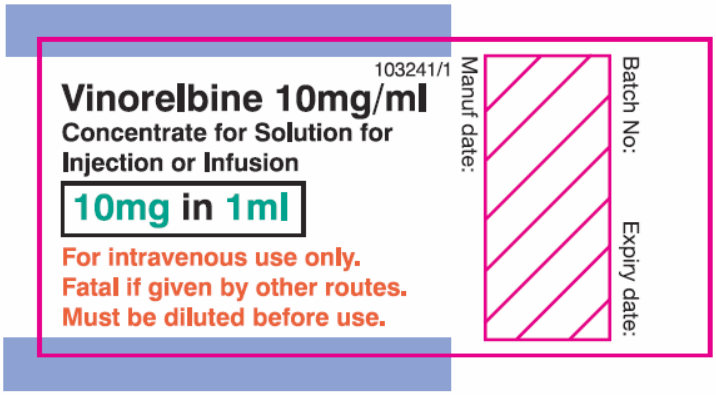
OVERPRINT AREA

BATCH NUMBER AND EXPIRY DATE
TO BE OVERPRINTED

VINORELBINE 10MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

PL 04543/0500

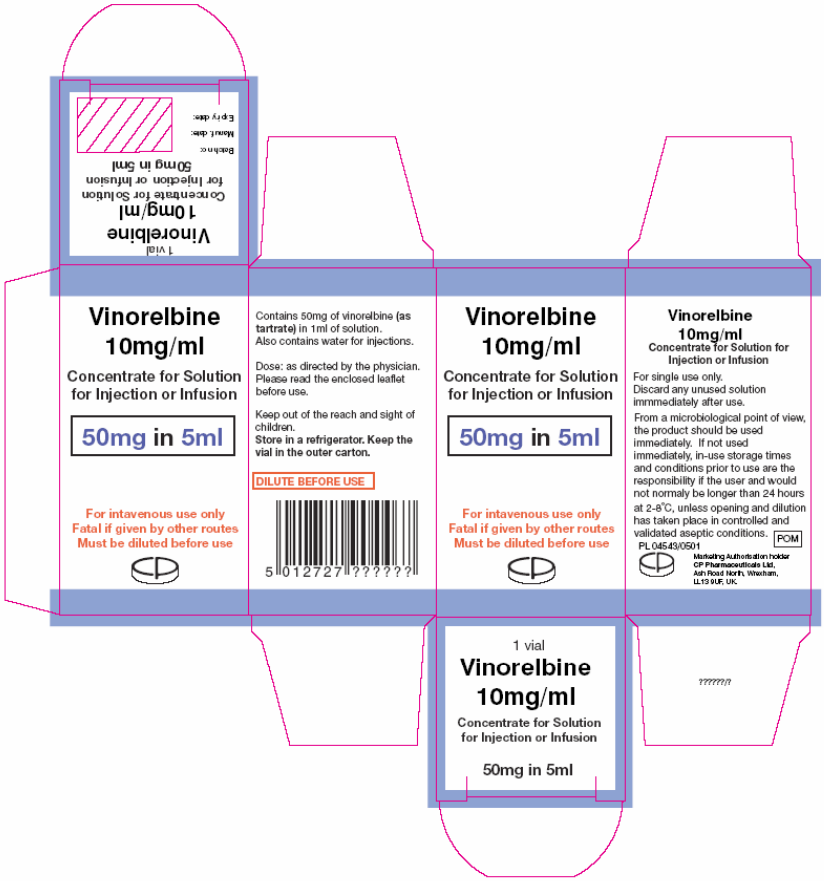
100%



300%

VINORELBINE 10MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

PL 04543/0501



OVERPRINT AREA

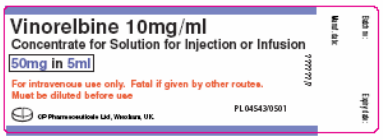
BATCH NUMBER AND EXPIRY DATE
TO BE OVERPRINTED

VINORELBINE 10mg/ml
Concentrate for Solution for injection or Infusion
5ml vial Carton
Version 6 Mock-up 10/01/06
Colour: Pantone 2716C, 2725C, Warm Red, Black
Size: 38mm x 38mm x 70mm

Vinorelbine 10mg/ml concentrate 5ml vial ctn.ai

VINORELBINE 10MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

PL 04543/0501



100%

Batch number and expiry date to be overprinted

VINORELBINE 10mg/ml
Concentrate for Solution for Injection or Infusion
5ml Vial LABEL

Colour: Pantone 2716, 2725C, Warm Red, Black
Size: 62mm x 21mm

Version 4 Mock-up 11/01/06

Mac file: Mock Ups:
Vinorelbine 10mg/ml Concentrate 5ml Vial **LBL**