VINORELBINE 10MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

PL 19364/0028

UKPAR

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VINORELBINE 10MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted UKR Regulatory Affairs Limited a Marketing Authorisation (licence) for the medicinal product Vinorelbine 10mg/ml Concentrate for Solution for Infusion (PL 19364/0028) on 30th July 2008. This is a prescription-only medicine 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 approved product was considered to be a generic version of the reference product Navelbine 10mg/ml Concentrate for Solution for Infusion (PL 00603/0028) licensed to Pierre Fabre Limited.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of using Vinorelbine 10mg/ml Concentrate for Solution for Infusion outweigh the risk; hence a Marketing Authorisation (MA) 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 MHRA granted UKR regulatory Affairs Limited a Marketing Authorisation for the medicinal product Vinorelbine 10mg/ml Concentrate for Solution for Infusion (PL 19364/0028) on 30th July 2008. The product is a prescription-only medicine (POM).

The application was submitted as an abridged national application, according to Article 10.1 of Directive 2001/83/EC, as amended. The application refers to the innovator product, Navelbine 10mg/ml Infusion (PL 00603/0028), licensed to Pierre Fabre Limited on 10th May 1996.

The drug product is a concentrate for solution for infusion containing 10mg/ml of the active ingredient vinorelbine tartrate. This product 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 mictotubules, 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 point following mitosis. The proposed indications for this product are the same as for the innovator product.

PHARMACEUTICAL ASSESSMENT

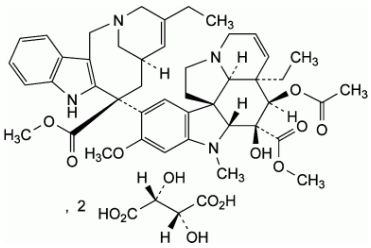
DRUG SUBSTANCE

Vinorelbine tartrate

INN: Vinorelbine tartrate
Chemical Name: Methyl (3aR, 4R, 5S, 5aR, 10bR, 13aR)-4-acetyloxy)-3a-ethyl-9[(8)-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-1 H-indolizinol[8,1-cd]carbazol-5-caroxylate (2R, 3S)-23-dihydroxybutanedioate

3',4'-Didehydro-4'-deoxy-8'-norvincaleukoblastine ditatrate

Structure:



Molecular formula: $C_{45}H_{54}N_4O_8.2C_4H_6O_6$
Molecular weight: 1079

Physical form: White to almost white powder hygroscopic
Solubility: Practically insoluble in hexane, freely soluble in methanol and in acetone.

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.

Satisfactory elemental analysis, MS, IR, ^{1}H NMR data are provided.

An appropriate specification based on the European Pharmacopoeia has been provided.

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

The active substance is stored in amber bottles flushed with nitrogen and packed in a food grade transparent polythene bag and placed in stainless steel container along with silica gel sachets and Styrofoam chips. Satisfactory specifications and certificates of analysis are provided.

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

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 6 months, when stored at appropriate storage instructions.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely sodium hydroxide and water for injection. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeial monograph. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contains material of animal or human origin. There were no novel excipients used and no overages.

Impurity Profiles

Impurity profiles for the drug product were found to be similar to those for the reference product.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Satisfactory process validation data have been provided on three commercial scale batches.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. 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 drug is distributed in glass vials (type I) of appropriated volume closed by a butyl or chlorobutyl stopper. The stopper is covered with a crimped-on aluminium cap equipped with a polypropylene seal. The product is packaged in vial sizes of 1 ml and 5 ml.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months has been set, which is satisfactory. Storage conditions are “Store at $2^{o}C – 8^{o}C$ (in a refrigerator)” and “Store in the original container in order to protect from light”. These are satisfactory.

Conclusion

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

PRECLINICAL ASSESSMENT

The application was submitted as a national, abridged, standard application, according to Article 10.1 of Directive 2001/83/EC, as amended.

No new preclinical data have been supplied with this application and none are required for an application of this type. A preclinical expert report has been written by a suitably qualified person and is satisfactory.

CLINICAL ASSESSMENT

1 INTRODUCTION

This is a generic application for Marketing Authorisation in the UK submitted under Article 10(1) of Directive 2001/83 (as amended) for a known active substance. The reference product is Navelbine 10mg/ml Infusion (PL00603/0028), authorised to Pierre Fabre on 10 May 1996.

2 OVERVIEW

An appropriate clinical overview has been included in the dossier. The clinical overview contains a sufficient outline of the published literature concerning the clinical pharmacology, efficacy and safety of vinorelbine tartrate.

3 BIOWAVER

The product proposed for marketing authorisation is to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference product Navelbine 10mg/ml Infusion. Thus, in accordance with the"Note for Guidance on the Investigation of Bioavailability and Bioequivalence", (CPMP/EWP/QWP/ 1401/98), the applicant is not required to submit a bioequivalence study.

4 CLINICAL STUDY REPORTS

This application is a generic application referring to the reference medicinal product is Navelbine 10mg/ml Infusion (PL00603/0028), authorised to Pierre Fabre on 10 May 1996 and has been authorised for more than 10 years in the UK. According to Article 10(1) of Directive 2001/83/EC, for this type of application, the applicant is not required to provide results of clinical trials.

5 PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPC is consistent with that for the innovator product and is satisfactory.

Patient Information Leaflet / Technical Information Leaflet

The approved PIL and technical leaflet are in line with the final SmPC and are satisfactory.

Labelling

Colour mock-ups of the labelling have been provided. The labelling is satisfactory.

6 ASSESSOR'S OVERALL CONCLUSIONS

The grounds for establishing the proposed product as a generic version of the reference product, Navelbine 10mg/ml Infusion (PL00603/0028), are considered adequate. The product literature is approved.

All issues have been adequately addressed by the applicant and sufficient clinical information has been submitted to support this application. When used as indicated, Vinorelbine 10mg/ml Concentrate for Solution for Infusion has a favourable benefit-to-risk ratio. Therefore, a Marketing Authorisation may be granted on medical grounds.

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 data were submitted and none are required for an application of this type.

EFFICACY

The applicant's Vinorelbine 10mg/ml Concentrate for Solution for Infusion has been demonstrated to be a generic version of the reference product Navelbine 10mg/ml Infusion (PL 00603/0028).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The approved SmPC, PIL, technical leaflet, and labelling are satisfactory and consistent with that for the innovator product.

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

The approved labelling artwork complies with statutory requirements.

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 tartrate is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

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STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 25th May 2007.
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 7th August 2007.
3	Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 31st August 2007 and 15th May 2008.
4	The applicant responded to the MHRA's requests, providing further information on 27th November 2007 and 2nd July 2008 for the quality sections.
5	The application was determined on 30th July 2008.

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

VINORELBINE 10MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

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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 1 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

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

A clear colourless 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 intra-thecal route is contra-indicated.

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 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.

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 1/3 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 1 week in about 35% of treatment courses.
The maximum tolerated dose per administration : 35.4mg/m^2
The maximum total dose per administration : 60 mg

4.3 CONTRAINDICATIONS

Pregnancy
Lactation
Severe hepatic insufficiency not related to the tumoural process
Known hypersensitivity to vinorelbine or other vinca alkaloids, or to any of the constituents.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

• Vinorelbine must only be administered by the intravenous route. **The use of intra-thecal route is contra-indicated**. 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 INTERACTION 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.
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 (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.
- Anaemia (G1-2 : 61.2%; G3-4 : 7.4%) and thrombocytopenia (G1-2 : 5.1%; G3-4 : 2.5%) are seldom severe.

•Neurological tolerance

- 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.

•Gastrointestinal tolerance

- 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.

•Allergic reactions

As with other vinca alkaloids, Vinorelbine may occasionally produce dyspnoea and bronchospasm and more rarely local or generalised cutaneous reactions. Anaphylactic shock has been reported.

•Venous tolerance

Burning pain at the injection site and local phlebitis (G1 : 12.3%; G2 : 8.2%; G3 : 3.6%; G4 : 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 (G1-2 : 21%; G3-4 : 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

• Studies of acute toxicity in animals :

The symptoms of overdose are pilo erection, 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.

• 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

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.

Safety and efficacy of Vinorelbine in paediatric patients have not been established. Clinical data from a single-arm study in 46 patients with recurrent solid tumours, including rhabdomyosarcoma / undifferentiated sarcoma, neuroblastoma, and CNS tumours, at doses similar to those used in adults showed no meaningful clinical activity. Toxicities were similar to those reported in adult patients.

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 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

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium Hydroxide

Water for Injection

6.2 INCOMPATIBILITIES

Vinorelbine solution (10mg/ml) 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 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

24months.
After diluting Vinorelbine in normal saline solution or dextrose solution, the product should be used either immediately or it can be stored in the clear glass vials or in the PVC perfusion bags for 24 hours in a refrigerator (+2°C to +8°C).

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at $2^oC – 8^oC$ (in a refrigerator). Store in the original container in order to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

The drug is distributed in glass vials (type I) of appropriated volume closed by a butyl or chlorobutyl stopper. The stopper is covered with a crimped-on aluminium cap equipped with a polypropylene seal.
Vials of 1 ml and 5 ml

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

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 cannula 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

UKR Regulatory Affairs Ltd.

Chiltern House

Thame Road

Haddenham

Bucks.

HP17 8BY

8 MARKETING AUTHORISATION NUMBER(S)

PL 19364/0028

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/07/2008

10 DATE OF REVISION OF THE TEXT

30/07/2008

11 DOSIMETRY (IF APPLICABLE)

Not applicable.

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Not applicable.

VINORELBINE 10MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION
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PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Vinorelbine 10 mg/ml concentrate for solution for infusion

Active substance: vinorelbine

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor 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 Sterile Concentrate* IS AND WHAT IT IS USED FOR?

Vinorelbine, the active ingredient of *Vinorelbine Sterile Concentrate*, belongs to the vinca alkaloid drug group. *Vinorelbine Sterile Concentrate* is used to treat certain types of **lung cancer** and **breast cancer**.

2. BEFORE YOU USE *Vinorelbine Sterile Concentrate*

Do not use *Vinorelbine Sterile Concentrate* - if you are **hypersensitive** (allergic) to vinorelbine or any other vinca alkaloids or to any of the other ingredients- if your **liver function** is severely impaired- if you are **pregnant** or are **breast-feeding**

Take special care with *Vinorelbine Sterile Concentrate*
- if you are undergoing radiotherapy which includes the liver
- if you have signs of infection, such as fever, chills, sore throat
Tell your doctor as soon as possible, so that he/she can perform any necessary tests.
- if you suffer from impaired liver function

Avoid all contact with the eyes, as there is a risk of severe irritation or even ulceration of the surface of the eye. If the medicine comes into contact with the eye, rinse immediately with saline solution.

Before and during treatment with *Vinorelbine Sterile Concentrate* your blood values will be checked. If your blood values are too low (neutrophile granulozytes below 2,000 per mm^3 blood), treatment will be interrupted until values are reached which allow further treatment with vinorelbine.

Children and adolescents under 18 years
Safety and efficacy have not been established in children and adolescents. Ask your doctor for advice.

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

Pregnancy and breast-feeding
You may not use *Vinorelbine Sterile Concentrate* if you are pregnant.
Please inform your doctor, if you become pregnant or think you may be pregnant.

You may not use *Vinorelbine Sterile Concentrate* if you are breast-feeding. If treatment becomes necessary, the infant must be weaned.

3. HOW TO USE *Vinorelbine Sterile Concentrate*
Vinorelbine Sterile Concentrate may be administered only under the supervision of a doctor experienced in the treatment of cancer. He/she defines dosage and duration of treatment.

Before and during treatment your blood values will be monitored.

The **usual adult dose** is **25–30 mg/m2 body surface area once per week**. The dose is also dependent upon your medical condition, your general state of health and whether you are also taking/using any other medicines at the same time.

The reconstituted solution is administered as a slow injection into a vein over a period of 5–10 minutes or as an infusion into a vein over a period of 20–30 minutes. After administration, the vein must be well flushed with isotonic saline solution.

If more *Vinorelbine Sterile Concentrate* was used than should
Your doctor will ensure that you receive the correct dose. If overdose occurs, more severe side effects can occur. Your doctor can treat these side effects symptomatically. Inform your doctor, if side effects occur.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, *Vinorelbine Sterile Concentrate* can cause side effects, although not everybody gets them.
These include nausea, vomiting, diarrhoea, constipation, "pins and needles", jaw pain and temporary hair loss, reduction in white blood cells, reduction in blood platelets, which increases the risk of bleeding or bruising, anaemia.
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.

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 Sterile Concentrate*

Keep all medicines out of the reach and sight of children.

Do not use this medicine after the expiry date which is stated on the outer carton and the label. The expiry date refers to the last day of that month.

Store in the refrigerator (2–8 °C).
Store in the original pack, in order to protect the contents from light.

Shelf life after opening or reconstitution
After dilution, the medicine can be stored at 25 °C or in the refrigerator (2–8 °C) for 24 hours.

6. FURTHER INFORMATION

What *Vinorelbine Sterile Concentrate* contains

The active substance is vinorelbine (as vinorelbine tartrate).
1 ml concentrate for solution for infusion contains 10 mg vinorelbine.
Every vial with 1 ml concentrate contains 10 mg vinorelbine.
Every vial with 5 ml concentrate contains 50 mg vinorelbine.
The other ingredients are sodium hydroxide and water for injections.

What *Vinorelbine Sterile Concentrate* looks like and contents of the pack
Vinorelbine Sterile Concentrate is a clear, colourless solution.

Vinorelbine Sterile Concentrate is available in packs containing 1 vial.

Marketing authorisation holder
UKR Regulatory Affairs Ltd
Chiltern House, Thame Road
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The following information is intended only for doctors or medical personnel:

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.

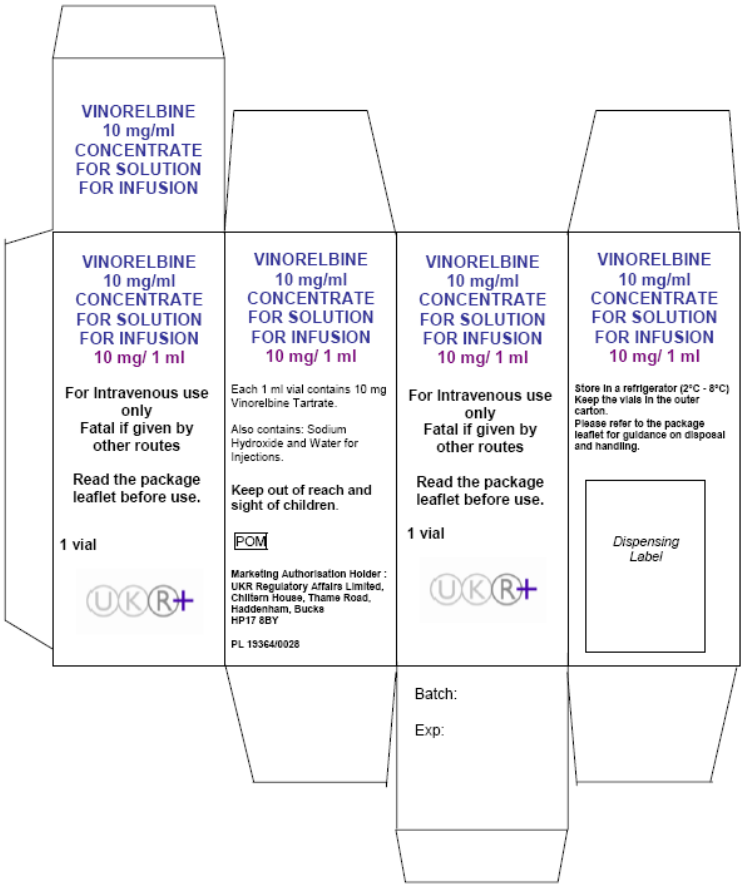
Vinorelbine must be given strictly intravenously : it is very important to make sure that the cannula is accurately placed in the vein before starting to infuse VINORELBINE.
If the drug extravasates during intravenous administration, a substantial local reaction may occur. In this case, the injection should be stopped and the rest of the dose should be administered in another vein.

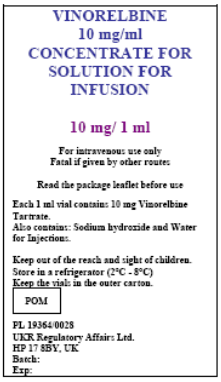
Disposal guidelines all sharps should be placed in an appropriate container and all other disposable items and cleaning materials in a sealed plastic bag which should be incinerated with other clinical waste.
Waste material may be disposed of by incineration.

VINORELBINE 10MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

PL 19364/0028
LABELLING

Carton- 10mg/ml- 1ml vial





Carton- 10mg/ml- 5ml vial