VINORELBINE 10 MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

(VINORELBINE TARTRATE)

PL 22191/0003 & 22191/0004

UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Sindan Limited Marketing Authorisations (licences) for the medicinal product Vinorelbine 10mg/ml Concentrate for Solution for Infusion (PL 22191/0003 & 0004) on 16th September 2008. This is a prescription-only medicine (POM) used to treat cancer.

Vinorelbine 10mg/ml Concentrate for Solution for Infusion contains the active ingredient, vinorelbine tartrate. Vinorelbine belongs to a family of medicines used to treat cancer called the vinca alkaloid family. Vinorelbine is intended for the treatment of cancer, specifically advanced non small cell lung cancer and advanced breast cancer.

The proposed products were considered to be generic versions of the reference product Navelbine 10mg/ml Concentrate for Solution for Infusion (PL 00603/0028, Pierre Fabre Limited), based on the data submitted by Sindan Limited.

These applications are based on a reference product with a valid UK licence. No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of using Vinorelbine 10mg/ml Concentrate for Solution for Infusion outweigh the risk, hence Marketing Authorisations have been granted.

VINORELBINE 10 MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

(VINORELBINE TARTRATE)

PL 22191/0003 & 22191/0004

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Sindan Limited Marketing Authorisations (licences) for the medicinal product Vinorelbine 10mg/ml Concentrate for Solution for Infusion (PL 22191/0003 & 0004) on 16th September 2008. The product is a prescription-only medicine (POM).

The applications were submitted as national, abridged applications, according to Article 10.1 of Directive 2001/83/EC, as amended. The applications refer to the innovator product, Navelbine 10mg/ml Concentrate for Solution for Infusion (PL 00603/0028), marketed by Pierre Fabre Limited and authorised on 10th May 1996.

The active substance, vinorelbine tartrate, is a vinca alkaloid with a broad spectrum of anti-tumour activity. Vinorelbine is a cytostatic antineoplastic drug, and is believed to act against tumour cells by binding to tubulin, the basic protein subunit of microtubules. This process inhibits microtubule assembly, causing dissolution of mitotic spindles and, ultimately, cell cycle arrest in metaphase of tumour cell division.

The pharmacokinetics of intravenously given vinorelbine has been shown to be linear to dosage levels of up to 45 mg/m^2. Vinorelbine binds moderately (13.5%) to plasma proteins, and greatly (78%) to thrombocytes. Vinorelbine has very good penetration of lung tissue (the tissue and plasma concentration ratio of the drug measured from biopsy was over 300).

Vinorelbine is metabolised mainly by the CYP3A4 enzyme. Intravenously administered vinorelbine is eliminated in a triphasic manner. The total clearance of vinorelbine is rapid (1.3 l/h/kg). Elimination occurs primarily through the bile; renal elimination is only a small part (18.5% of marker was excreted in urine). The terminal half-life in plasma is over 40 hours.

Vinorelbine is indicated 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 used in the treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen.

These applications for Vinorelbine 10mg/ml Concentrate for Solution for Infusion were submitted at the same time and, consequently, all sections of the Scientific Discussion refer to both products.

PHARMACEUTICAL ASSESSMENT

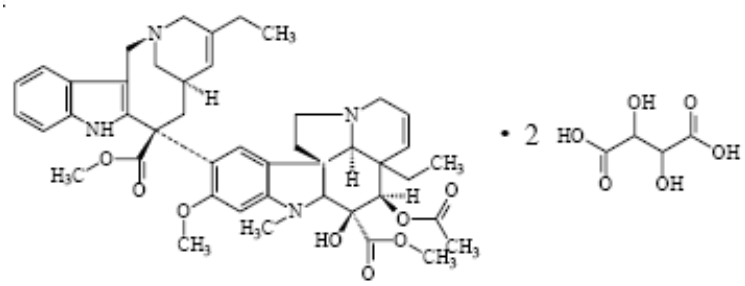
ACTIVE SUBSTANCE

Vinorelbine tartrate

Nomenclature:

INN:	Vinorelbine tartrate
Chemical name:	Methyl (3a*R*,4*R*,5*S*,5a*R*,10b*R*,13a*R*)-4-(acetyloxy)-3a-ethyl-9-[(6*R*,8*S*)-4-ethyl-8- (methoxycarbonyl)-1,3,6,7,8,9-hexahydro-2,6-methano-2*H*-azacyclodecino[4,3-*b*]indol-8-yl]-5-hydroxy-8-methoxy-6-methyl-3a,4,5,5a,6,11,12,13a-octahydro-1*H*-indolizino[8,1-*cd*]carbazole-5-carboxylate dihydrogen bis[(2*R*,3*R*)-2,3- dihydroxybutanedioate].

Structure:



Molecular formula:	$C_{45}H_{54}N_4O_8$, $2(C_4H_6O_6)$
Molecular weight:	1079
CAS No:	125317-39-7
Physical form:	A white or almost white powder, hygroscopic
Solubility:	Freely soluble in water and in methanol, practically insoluble in hexane

The active substance, vinorelbine tartrate, is the subject of a European Pharmacopeia (EP) monograph.

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 specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin, and therefore comply with the TSE requirements. A satisfactory Certificate of Analysis has been provided for the primary reference standards used by the active substance manufacturer during validation studies.

An appropriate active substance specification has been provided which complies with the EP monograph specification, but with additional in-house microbiological requirements. Satisfactory details have been provided for the compendial and non-compendial test methods. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

The active substance is stored in appropriate packaging. It is packed in two-layer polyethylene (PE) bags, filled with an inert gas and heat-sealed. The sealed PE bags are then placed inside aluminium foil bags and also heat-sealed filled with an inert gas. The bags are then placed in aluminium tins. Specifications and Certificates of Analysis for all packaging components used have been provided. The polyethylene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for active substance stored in the proposed packaging. This data demonstrates the stability of the active substance and supports a retest period of 12 months, when stored in the proposed packaging. The storage conditions are “Under nitrogen atmosphere, protected from light, at a temperature not exceeding -15°C (freezer)”.

DRUG PRODUCT

Description & Composition

The drug products are presented in glass vials as a clear, colourless to slightly yellow, solution for infusion, containing a 10mg/ml concentration of vinorelbine that has to be diluted before being given to you.

The only other ingredient is the pharmaceutical excipient, water for injections. Appropriate justification for the inclusion of this excipient has been provided.

The water for injections complies with its European Pharmacopoeia monograph, and a satisfactory Certificate of Analysis has been provided for it.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product.

There were no novel excipients used.

There is an overfill of the vials of 14% for the 10mg/1ml pack, corresponding to 11.4mg vinorelbine base/1.14ml solution; and 6% for the 50mg/5ml, corresponding to 53mg vinorelbine base/5.3ml solution. The overfills are required to obtain the extractable volume stated on the vial. This is acceptable.

Impurity profiles

A satisfactory impurity profile was presented and the impurities were within the specification limits.

Pharmaceutical development

Details of the pharmaceutical development of the drug products have been supplied and are satisfactory.

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. Process validation studies have been conducted and are satisfactory.

Finished product specification

The finished product specifications proposed for both release and shelf life are acceptable, and provide an assurance of the quality and consistency of the finished products. 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 all primary reference standards used.

Container Closure System

The drug product is packed in Type I transparent glass vials of size 1ml and 5ml, containing 10mg and 50mg vinorelbine respectively in a 10mg/ml strength solution. The vials are sealed with bromobutyl rubber stoppers and aluminium flip-off caps. The vials are packaged individually, with the product information leaflet, in cardboard outer cartons.

Specifications and Certificates of Analysis for all packaging components used have been provided, and are satisfactory. All primary packaging satisfies Directive 2002/72/EC (as amended), and is suitable for contact with parenteral preparations.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 30 months has been set, with storage instructions ‘Store in a refrigerator (2°C - 8°C). Keep the vial in the outer carton in order to protect from light. Do not freeze.’. This is satisfactory. For shelf-life and storage conditions of the diluted medicinal product, please refer to the SPC.

Bioequivalence Study

A bioequivalence study is not necessary to support these applications for a parenteral product.

EXPERT REPORT

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

PRODUCT INFORMATION:

The approved SmPCs, leaflet, and labelling are satisfactory. Colour mock-ups of the labelling have been provided.

Conclusion

The proposed product, Vinorelbine 10mg/ml Concentrate for Solution for Infusion, has been shown to be a generic version of the reference product, Navelbine 10mg/ml Concentrate for Solution for Infusion, with respect to qualitative and quantitative content of the active substance, and the pharmaceutical form. The test product is pharmaceutically equivalent to the reference product, which has been licensed in the UK for over 10 years. Given the route of administration and pharmaceutical form, it is not necessary to demonstrate bioequivalence of the proposed product to the reference product.

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. It is recommended that Marketing Authorisations are granted.

PRECLINICAL ASSESSMENT

The applications were submitted as national, abridged, applications, according to Article 10.1 of Directive 2001/83/EC, as amended.

No new preclinical data have been supplied with these applications and none are required for applications of this type. A preclinical overview has been written by a suitably qualified person and is satisfactory.

CLINICAL ASSESSMENT

INDICATIONS

Vinorelbine 10mg /ml Concentrate for Solution for Infusion is indicated 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 used in the treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen.

The indications are consistent with those for the innovator product and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

The posology is consistent with that for the innovator products and is satisfactory.

TOXICOLOGY

No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY

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

Pharmacodynamics

Vinorelbine belongs to the group of drugs known as vinca alkaloïds and analogues (ATC Code L01C A04).

Vinorelbine is an antineoplastic drug of the vinca alkaloid family but unlike all the other vinca alkaloids, the catharantine moiety of vinorelbine has been structurally modified. At the molecular level, it acts on the dynamic equilibrium of tubulin in the microtubular apparatus of the cell. It inhibits tubulin polymerization and binds preferentially to mitotic microtubules, affecting axonal microtubules at high concentrations only. 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.

Pharmacokinetics

Vinorelbine has high affinity for platelets and lymphocytes. Binding to plasma protein is low (13.5% of the total blood-bound vinorelbine). 78% of the total blood-bound vinorelbine was associated with platelets and 4.8% of the total blood-bound vinorelbine was associated with lymphocytes.

There is significant uptake of vinorelbine in the lungs, as assessed by surgical lung biopsies, which showed concentrations up to 300-fold higher than in serum.

Biotransformation: Vinorelbine is principally metabolised by cytochrome P450 3A4. All metabolites have been identified and none is active, except 4-O-deacetyl vinorelbine, which is the main metabolite in blood. No sulphonic or glucuronic conjugates are found.

Elimination: The mean terminal half-life of vinorelbine is around 40hours. Blood clearance is high, approaching hepatic blood flow, and is 0.72 l/h/kg on average (range: 0.32 – 1.26 l/h/kg).

Renal elimination is low (< 20% of the intravenous dose administered) and consists mostly of the in parent compound. Biliary excretion is the predominant elimination route of unchanged vinorelbine, which is the main recovered compound, and its metabolite 4-O-deacetyl vinorelbine.

EFFICACY

No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical overview.

Vinorelbine 10mg/ml Concentrate for Solution for Infusion is to be administered as an aqueous intravenous solution and contains the same active substance, in the same concentration, as the currently authorised reference product Navelbine 10mg/ml. 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.

SAFETY

No new data are submitted and none are required for this type of application. Safety is reviewed in the clinical overview.

EXPERT REPORT

The expert overview on the clinical aspect of the product proposed for marketing was satisfactory. The clinical overview contains a sufficient outline of the published literature concerning the clinical pharmacology, efficacy and safety of vinorelbine tartrate. The report was prepared by an appropriately qualified expert for whom a satisfactory CV has been supplied.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPCs are consistent with those for the reference product and are acceptable.

Patient Information Leaflet (PIL)

The PIL is in line with the approved SmPCs and is satisfactory.

Labelling

The labelling is satisfactory.

CONCLUSION

The grounds for establishing the proposed product as a generic version of the reference product, Navelbine 10mg/ml Concentrate for Solution for Infusion (PL 00603/0028), are considered adequate. The product literature is approved.

Sufficient clinical information has been submitted to support this application. When used as indicated, Vinorelbine10mg /ml Concentrate for Solution for Infusion has a favourable benefit-to-risk ratio. Therefore, the grant of a Marketing Authorisation was recommended 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 applications of this type.

EFFICACY

The applicant's Vinorelbine 10mg/ml Concentrate for Solution for Infusion (PL 22191/0003 & 0004) have been demonstrated to be generic versions of the reference product, Navelbine 10mg /ml Concentrate for Solution for Infusion (PL 00603/0028, Pierre Fabre Limited).

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

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

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet 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. The qualitative and quantitative assessment supports the claim that the applicant's product and the innovator product are interchangeable. 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.

VINORELBINE 10 MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

(VINORELBINE TARTRATE)

PL 22191/0003 & 22191/0004

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation applications on 29th July 2005

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 30th September 2005

3 Following assessment of the applications the MHRA requested further information relating to the clinical dossier on 7th July 2006 and further information relating to the quality dossier on 15th August 2006

4 The applicant responded to the MHRA's request, providing further information for the quality sections on 19th March 2007 and further information for the clinical sections on 25th June 2007

5 Subsequently, the MHRA requested further information relating to the applications on 25th June 2007

6 The applicant responded to the MHRA's request, providing further information on 26th October 2007

7 The applications were determined on 10th September 2008

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Vinorelbine 10mg/ml Concentrate for Solution for Infusion is as follows (for both 22191/0003 & 0004):

1 NAME OF THE MEDICINAL PRODUCT

Vinorelbine 10 mg/ ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml concentrate for solution for infusion contains 10mg vinorelbine base equivalent to 13.85mg vinorelbine tartrate .

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

For PL 22191/0004, the above sentence reads:

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

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

Vinorelbine 10 mg/ml concentrate for solution for infusion is a clear, colourless to slightly 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 after appropriate dilution.

The use of intrathecal route is contra-indicated.

Administration should always be followed by a normal saline infusion to flush the vein.

Instructions for use and handling: see section 6.6.

In adults :

Vinorelbine is usually given at 25-30mg/m² weekly.

Vinorelbine may be administered by slow bolus (5-10 minutes) after dilution in 20-50 ml of sodium chloride 9 mg/ml (0.9%) solution for injection or in 5% glucose solution for injection. Administration should always be followed with at least 250 ml of an isotonic solution to flush the vein.

Advanced non-small cell lung cancer and advanced breast cancer

- In monotherapy the usual dose given is 25-30 mg/m² once weekly.

- In combination chemotherapy the usual dose (25-30 mg/m²) is usually maintained, while the frequency of administration is reduced e.g. day 1 and 5 every 3 weeks or day 1 and 8 every 3 weeks according to treatment protocol.

Elderly

See section 5.2: Pharmacokinetic properties.

Impaired hepatic function:

For patients presenting with severe liver impairment (bilirubin > 2xUNL and/or transaminases > 5xUNL), it is suggested that the dose be reduced by 33% and the haematological parameters be closely monitored since the maximum dose which was evaluated in this subset of patients was 20mg/m^2.

See sections: 4.4: Special warnings and precautions for use

5.2: Pharmacokinetic properties

Impaired renal function:

For patients with impaired kidney function, there is no need to adjust the dosage.

See section 4.4: Special warnings and precautions for use.

Paediatric patients

Vinorelbine is not recommended for use in children due to a lack of data on safety and efficacy: see section 5.1: Pharmacodynamic properties

Dosage adjustment in specific patient groups: see section 4.4 Special warnings and precautions for use.

4.3 CONTRAINDICATIONS

- Known hypersensitivity to vinorelbine or other vinca alkaloids, or to any of the constituents.

- Pregnancy [see section 4.6]

- Lactation [see section 4.6]

- Neutrophil count < 1500/mm3 or severe infection current or recent (within 2 weeks)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Special warnings

Vinorelbine must only be administered by the intravenous route.

The use of intrathecal route is contra-indicated.

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

Since inhibition of the hematopoietic system is the main risk associated with Vinorelbine, close haematological monitoring should be undertaken during treatment (determination of haemoglobin level and the leucocyte, neutrophil and platelet counts on the day of each new administration). The dose limiting adverse reaction is mainly neutropenia. This effect is non-cumulative, having its nadir between 7 and 14 days after the administration and is rapidly reversible within 5 to 7 days. If the neutrophil count is below 1500/mm^3 and/or the platelet count is below 75000/ mm^3 then the treatment should be delayed until recovery.

If the patient presents signs or symptoms suggestive of infection, a prompt investigation should be carried out.

Precautions

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

The pharmacokinetics of Vinorelbine is not modified in patients presenting with moderate or severe liver impairment. For dosage adjustment in this specific patient group see section 4.2.

As there is a low level of renal excretion there is no pharmacokinetic rationale for reducing Vinorelbine dose in patients with impaired kidney function.

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 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 of Vinorelbine with other drugs with known bone marrow toxicity is likely to exacerbate the myelosuppressive adverse effects. However the incidence of granulocytopenia associated with Vinorelbine use in combination with cisplatin is higher than associated with Vinorelbine single agent.

As CYP 3A4 is mainly involved in the metabolism of Vinorelbine, combination with inducers or inhibitors of this isoenzyme might modify the pharmacokinetics of Vinorelbine

The combination Vinorelbine - cisplatin shows no interaction on pharmacokinetic parameters.

4.6 PREGNANCY AND LACTATION

Pregnancy

- Vinorelbine is suspected to cause serious birth defects when administered during pregnancy: see section 5.3.

- Vinorelbine is contraindicated in pregnancy: see section 4.3 contraindications.

- If pregnancy occurs during treatment, genetic counselling should be offered.

Women of childbearing potential

Women of child-bearing potential have to use effective contraception during treatment and up to 3 months after treatment: see section 4.3 contraindications.

Breast feeding

- It is unknown whether Vinorelbine is excreted in human breast milk.

- The excretion of Vinorelbine in milk has not been studied in animal studies.

- A risk to the suckling child cannot be excluded therefore breast feeding must be discontinued before starting treatment with Vinorelbine: see section 4.3 contraindications.

Fertility

Men being treated with Vinorelbine are advised not to father a child during and up to 3 months after treatment: see section 4.3 contraindications.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed.

On the basis of the vinorelbine pharmacodynamic profile, Vinorelbine is unlikely to impair the ability to drive or operate machinery. However, caution is necessary in patients treated with Vinorelbine considering some side effects of the drug [see section 4.8].

4.8 UNDESIRABLE EFFECTS

Adverse reactions reported as more than isolated cases are listed below, by system organ class and by frequency.

Frequencies are defined as: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥ 1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000) according to the MedDRA frequency convention and system organ classification.

See table of adverse reactions

Infections and infestations

Common:
- Infection bacterial, viral or fungal at different sites.

Uncommon:
- Septicaemia [very rarely fatal].

Blood and lymphatic system disorders:

Very Common :
- Bone marrow depression resulting mainly in neutropenia reversible within 5 to 7 days and noncumulative over time.

Common :
- Anaemia.
- Thrombocytopenia.

Immune system disorders

Rare:
- Systemic allergic reactions reported as anaphylactic shock, anaphylaxis and anaphylactoid type reactions .

Endocrine disorders

Very rare:
- SIADH: Inappropriate antidiuretic hormone secretion.

Metabolism and nutrition disorders

Rare:
- Severe hyponatraemia.

Nervous system disorders

Common:
- Neurologic disorders including loss of deep tendon reflexes.
- Weakness of the lower extremities has been reported after a prolonged chemotherapy.

Uncommon:
- Severe paresthesias with sensory and motor symptoms. These effects are generally reversible upon discontinuation of treatment..

Cardiac disorders

Rare:
- Ischemic heart disease: angina pectoris, myocardial infarction.

Very rare:
- Tachycardia, palpitation and heart rhythm disorders.

Vascular disorders

Uncommon:
- Hypotension.
- Hypertension.
- Flushing and peripheral coldness.

Rare:
- Severe hypotension.
- Collapse.

Respiratory system, thoracic and mediastinal disorders

Uncommon:
- Dyspnoea and bronchospasm may occur in association with Vinorelbine treatment.

Rare:
- Interstitial pneumonopathies have been reported in particular in patients treated with Vinorelbine in combination with mitomycin.

Gastrointestinal disorders

Very Common:
- Stomatitis.
- Nausea and vomiting.

Common:
- Constipation.
- Diarrhoea.

Rare:
- Paralytic ileus, treatment may be resumed after recovery of normal bowel mobility.
- Pancreatitis.

Hepatobiliary disorders

Very common:
- Transient elevations of liver function tests without clinical symptoms were reported.

Skin and subcutaneous tissue disorders

Common:
- Alopecia, usually mild in nature, may occur.

Rare:
- Generalized cutaneous reactions.

Musculoskeletal, connective tissue and bone disorders

Common:
- Arthralgia including jaw pain and myalgia.

General disorders and administration site conditions:

Common:
- Fatigue, fever, pain at different locations including chest pain and pain at the tumour site.
- Reactions at the injection site may include erythema, burning pain, vein discolouration and local phlebitis.

Rare:
- Local necrosis has been observed. Proper positioning of the intravenous needle or catheter and bolus injection followed by liberal flushing of the vein can limit these effects.

Adverse reactions reported as more than isolated cases are listed below, by system organ class and by frequency.

Frequencies are defined as:

very common (> 1/10), common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100), rare (> 1/10,000, < 1/1,000), very rare (< 1/10,000).

System Organ Classes **(MedDRA classification)**	**Very common** **(>10%)**	**Common** **(>1/100 and ≤ 1/ 10)**	**Uncommon** **(>1/1,000 and ≤ 1/100)**	**Rare** **(>1/10,000, < 1/1,000)**	**Very rare** **(< 1/10,000).**
Infections and infestations		Infection bacterial, viral or fungal at different sites	Severe sepsis with other visceral failure.	Septicaemia	Septicaemia complicated Septicaemia fatal
Blood and lymphatic system disorders	Bone marrow depression Neutropenia	Anaemia Thrombocytopenia			
Immune system disorders				Systemic allergic reactions reported as anaphylaxis, anaphylactic shock or anaphylactoïd type reactions	
Endocrine disorders					SIADH: Inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders			Hyponatraemia		
Nervous system disorders		Loss of deep tendon reflexes Reversible weakness of lower extremities	Paresthesia with sensory and motor symptoms		
Cardiac disorders				Ischemic cardiac disease Angina pectoris Myocardial infarction	Tachycardia Palpitations Heart rhythm disorders
System Organ Classes **(MedDRA classification)**	**Very common** **(> 10%)**	**Common** **(> 1/100 and ≤ 1/ 10)**	**Uncommon** **(> 1/1,000 and ≤ 1/100)**	**Rare** **(> 1/10,000, < 1/1,000)**	**Very rare** **(< 1/10,000).**

Vascular disorders			Hypotension, Hypertension, Flushing, Peripheral coldness.	Severe hypotension, Collapse	
Respiratory, thoracic and mediastinal disorders			Dyspnoea Bronchospasm	Interstitial pneumopathies	
Gastrointestinal disorders	Nausea Vomiting Stomatitis	Diarrhoea Constipation		Paralytic ileus Pancreatitis	
Hepatobiliary disorders	Transient elevations of liver function tests				
Skin and subcutaneous tissue disorders		Alopecia		Generalized cutaneous reactions	
Musculoskeletal, connective tissue and bone disorders.		Arthralgia, jaw pain Myalgia			
General disorders and administration site conditions		Fatigue, Fever, Infections. Pain at different sites, chest pain and pain at tumour site <u>Reactions at injection site as:</u> Erythema Burning pain Vein discoloration Local phlebitis		Local necrosis	

4.9 OVERDOSE

Accidental overdosages have been reported in humans : they may produce a period of bone marrow aplasia sometimes associated with infection, fever, paralytic ileus. General supportive measures together with blood transfusion and broad spectrum antibiotic therapy should be instituted as deemed necessary by the physician.

There is no known antidote for overdosage of Vinorelbine.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC Code: L01C A04 (Vinca alkaloïds and analogues)

Vinorelbine is an antineoplastic drug of the vinca alkaloid family but unlike all the other vinca alkaloids, the catharantine moiety of vinorelbine has been structurally modified. At the molecular level, it acts on the dynamic equilibrium of tubulin in the microtubular apparatus of the cell. It inhibits tubulin polymerization and binds preferentially to mitotic microtubules, affecting axonal microtubules at high concentrations only. 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

Pharmacokinetic parameters of vinorelbine were evaluated in blood.

Distribution

The steady-state volume of distribution is large, on average 21.2 l/h/kg (range: 7.5-39.7 l/h/kg), which indicates extensive tissue distribution.

Vinorelbine has high affinity for platelets and lymphocytes. Binding to plasma protein is low (13.5% of the total blood-bound vinorelbine). 78% of the total blood-bound vinorelbine was associated with platelets and 4.8% of the total blood-bound vinorelbine was associated with lymphocytes.

There is significant uptake of vinorelbine in the lungs, as assessed by surgical lung biopsies, which showed concentrations up to 300-fold higher than in serum. Vinorelbine is not found in the central nervous system.

Biotransformation

Vinorelbine is principally metabolised by cytochrome P450 3A4. All metabolites have been identified and none is active, except 4-O-deacetyl vinorelbine, which is the main metabolite in blood. No sulphonic or glucuronic conjugates are found.

Elimination

The mean terminal half-life of vinorelbine is around 40hours. Blood clearance is high, approaching hepatic blood flow, and is 0.72 l/h/kg on average (range: 0.32 – 1.26 l/h/kg).

Renal elimination is low (< 20% of the intravenous dose administered) and consists mostly of the in parent compound. Biliary excretion is the predominant elimination route of unchanged vinorelbine, which is the main recovered compound, and its metabolite 4-O-deacetyl vinorelbine.

Special patient groups

Renal impairment

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

Liver impairment

A first study has reported the effects of liver impairment on vinorelbine pharmacokinetics. This study was performed in patients with liver metastases due to breast cancer, and concluded that a change in mean clearance of vinorelbine was only observed when more than 75% of the liver is involved.

A phase I pharmacokinetic dose-adjusted study was conducted in cancer patients with liver dysfunction : 6 patients with moderate dysfunction (Bilirubin < 2 x UNL and Transaminases < 5 x UNL) treated up to 25 mg/m² and 8 patients with severe dysfunction (Bilirubin > 2 x UNL and/or Transaminases > 5 x UNL) treated up to 20 mg/m². Mean total clearance in these two subsets of patients was similar to that in patients with normal hepatic function. Therefore, the pharmacokinetics of vinorelbine are not modified in patients presenting with moderate or severe liver impairment. Nevertheless, in a conservative approach it is suggested that the dose be reduced by 33% and the haematological parameters closely monitored in patients with severe liver impairment since the maximum dose which was given in this subset of patients was 20 mg/m^2.

Elderly patients

Study on oral vinorelbine in elderly patients (≥ 70 years) with NSCLC demonstrated there is no influence of the age on vinorelbine pharmacokinetics and that no dose reduction is required.

PK-PD relation

A strong relationship has been demonstrated between vinorelbine blood exposure and of leucocytes or PMNs decreases.

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 shown that no haemodynamic effects have been found using a maximal tolerated dose in dogs, however only some non significant disturbances of repolarization 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 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 10 mg/ml concentrate for solution for infusion should not be diluted in alkaline solutions (risk of precipitate)

• In case of polychemotherapy, Vinorelbine 10 mg/ml concentrate for solution for infusion should not be mixed with other agents.

• Vinorelbine 10 mg/ml concentrate for solution for infusion is not absorbed to or affected by either PVC or clear neutral glass.

6.3 SHELF LIFE

As packaged for sale

30 months.

After opening

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

Shelf-life after dilution

The physicochemical and microbiological stability of the drug product after dilution in the recommended solutions for infusion (see section 6.6) has been demonstrated for 24 hours 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 are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions."

6.4 SPECIAL PRECAUTIONS FOR STORAGE

As packaged for sale

Store in a refrigerator (2°C - 8°C). Keep the vial in the outer carton in order to protect from light.

Do not freeze.

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

6.5 NATURE AND CONTENTS OF CONTAINER

Type I glass vials with bromobutyl rubber stoppers containing 10 mg vinorelbine in 1 ml solution or 50 mg vinorelbine in 5 ml solution. The vials are available individually packaged in a carton folding box.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Vinorelbine 10 mg/ml concentrate for solution for infusion has a more or less yellow colouration which does not affect the quality of the product.

Handling guidelines: the preparation and administration of Vinorelbine 10 mg/ml concentrate for solution for infusion 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 0.9% Sodium Chloride solution should be undertaken if any contact occurs.

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

Vinorelbine 10 mg/ml concentrate for solution for infusion may be administered by slow bolus (5-10 minutes) after dilution in 20-50 ml of 0.9% Sodium Chloride solution or by a short infusion (20-30 minutes) after dilution in 125 ml of 0.9% Sodium Chloride solution. Administration should always be followed by a 0.9% Sodium Chloride infusion to flush the vein.

Vinorelbine 10 mg/ml concentrate for solution for 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 the solution.

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.

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

7 MARKETING AUTHORISATION HOLDER

SINDAN Ltd.

81/ 8 Shepherds Hill

London N6 5RG

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 22191/ 0003 or 0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/09/2008

10 DATE OF REVISION OF THE TEXT

16/09/2008

PATIENT INFORMATION LEAFLET

Sindan

PACKAGE LEAFLET

VINORELBINE 10 mg/ml-concentrate for solution for infusion
VINORELBINE TARTRATE

PATIENT INFORMATION LEAFLET
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 further questions, ask your doctor.*
- *This medicine has been prescribed for you personally and you should 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.*

In this leaflet:

1. WHAT VINORELBINE IS AND WHAT IT IS USED FOR?
Vinorelbine belongs to a family of medicines used to treat cancer called the vinca alkaloid family.
Vinorelbine is intended for the treatment of cancer, specifically advanced non small cell lung cancer and advanced breast cancer.

2. BEFORE YOU USE VINORELBINE
You should not be given Vinorelbine
- If you are pregnant or think that you might be pregnant
- If you are breast feeding

Using other medicines
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those bought without a prescription.
Vinorelbine should not be given together with radiotherapy if the area treated includes the liver.

3. HOW TO USE VINORELBINE
Vinorelbine is always administered intravenously after appropriate dilution.
Vinorelbine will always be given by a healthcare professional. It is usually given once a week and usually at the rate of 25-30mg/m^2 per week. It may be by injection over a 5 to 10 minute period or by infusion over 20 to 30 minutes.
In combination chemotherapy the usual dose is usually maintained, while the frequency of administration is reduced.
In patients with impaired liver function the dose may be reduced.
After being given the drug your vein will be flushed with 0.9% Sodium Chloride so that the drug is dispersed.
Your doctor will perform regular tests to monitor your medical condition during your treatment and before each administration of Vinorelbine.
Vinorelbine is not recommended for use in children.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Vinorelbine can have side effects. Please report any side effects to your doctor. Some side effects that have been reported following treatment with vinorelbine are listed below.
Very common (occur in more than 1 in 10 users):
Bone marrow depression, neutropenia (a reduction in a type of white blood cell), inflammation of the mouth (stomatitis), nausea and vomiting, transient elevations of liver function tests.

- If you have a low neutrophil (a type of white blood cell) count or have (or have recently had) a severe infection

Take special care with Vinorelbine
Before each administration of Vinorelbine, a blood test will be done. If the results are not satisfactory, your treatment may be delayed and further checks made until the results return to normal. If you have signs or symptoms that suggest an infection (fever, chills, joint pain, etc...), tell your doctor immediately. Other tests may be needed.
If you have received radiotherapy where the treatment field includes the liver let your doctor know.
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 0.9% Sodium Chloride solution should be undertaken if any contact occurs.

Pregnancy
If you are pregnant, think you may be pregnant or become pregnant, tell your doctor immediately. You should not receive Vinorelbine during pregnancy. Women of childbearing potential must use effective contraception during treatment and for 3 months after treatment.

Fertility
Men being treated with Vinorelbine are advised not to father a child during and up to 3 months after treatment.

Breast feeding
You should not breast feed while you are being treated with Vinorelbine. Do not restart breast feeding until your doctor tells you it is safe to do so.

Driving and using machines
There is no reason why you cannot continue driving between courses of Vinorelbine, although care should be taken if you experience side effects

Common (occur in less than 1 in 10 users):
Infection - bacterial, viral or fungal at different sites. Anaemia, low blood platelet count (thrombocytopenia), loss of deep tendon reflexes, reversible weakness of the lower extremities, constipation, diarrhea, alopecia, joint pain, jaw pain, muscle pain, fatigue, fever, infections. Pain at different sites - chest pain and pain at tumour site. Reactions at injection site as: redness of the skin, burning pain, vein discoloration, local vein inflammation.
Uncommon (occur in less than 1 in 100 users):
Severe whole-body inflammation with other organ failure, low plasma sodium level, 'pins and needles' with sensory and motor symptoms, low blood pressure, high blood pressure, flushing, peripheral coldness, shortness of breath, coughing.
Rare (occur in less than 1 in 1000 users):
Blood poisoning (septicaemia), allergic reactions and anaphylactic shock, ischemic heart disease, angina, heart attack, severe low blood pressure, collapse, interstitial pneumopathies, bowel obstruction, inflammation of the pancreas (pancreatitis), generalized skin reactions, local necrosis.
Very rare (occur in less than 1 in 10,000 users:
Complicated or fatal blood poisoning (septicaemia), SIADH: Inappropriate antidiuretic hormone secretion, rapid heart beat, palpitations, heart rhythm disorders

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING VINORELBINE
This medicine will be stored in the pharmacy and made up in a special area before the doctor or nurse gives it to you.
Store in a refrigerator (2°C - 8°C).
Keep the vial in the outer carton in order to protect from light.
Do not freeze.
The physicochemical and microbiological stability of the drug product after dilution in the recommended solutions for infusion has been demonstrated for 24

hours at 2-8°C. From the microbiological point of view, the product must be used immediately after dilution. Other in-use time periods and other in-use storage conditions are the responsibility of the user.
An expiry date is given on the outer carton and the vial label. It should not be used after this date.

6. OTHER INFORMATION

The active ingredient is vinorelbine (as tartrate) 10 mg/ ml.
Each 1 ml vial contains a total content of 10mg vinorelbine (as tartrate).
Each 5 ml vial contains a total content of 50mg vinorelbine (as tartrate).
Vinorelbine 10 mg/ml concentrate for solution for infusion is a clear, colourless to slightly yellow solution. The other ingredient is water for injections.
Vinorelbine 10 mg/ml concentrate for solution for infusion has to be diluted before being given to you.

UK MARKETING AUTHORISATION HOLDER:
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81/8 Shepherds Hill
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United Kingdom

MANUFACTURER:
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MEDICAL INFORMATION LEAFLET

VINORELBINE 10 mg/ml-concentrate for solution for infusion

VINORELBINE TARTRATE

DATE OF LAST REVISION: September 2007

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PLEASE DETACH BEFORE HANDING ABOVE SECTION TO THE PATIENT

INFORMATION FOR HEALTH PROFESSIONALS

Below is a summary of information to assist in the administration of Vinorelbine. You should be experienced in the handling and use of cytotoxic agents and be familiar with the SPC for Vinorelbine. Reference should be made to guidelines on the safe handling of antineoplastic agents.

Preparation of Infusion

Vinorelbine 10 mg/ml concentrate for solution for infusion has a more or less yellow colouration which does not affect the quality of the product.

Handling guidelines: The preparation and administration of Vinorelbine 10 mg/ml concentrate for solution for infusion 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 0.9% Sodium Chloride solution should be undertaken if any contact occurs.

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

Vinorelbine 10 mg/ml concentrate for solution for infusion may be administered by slow bolus (5-10 minutes) after dilution in 20-50 ml of 0.9% Sodium Chloride solution or by a short infusion (20-30 minutes) after dilution in 125 ml of 0.9% Sodium Chloride solution. Administration should always be followed by a 0.9% Sodium Chloride infusion to flush the vein.

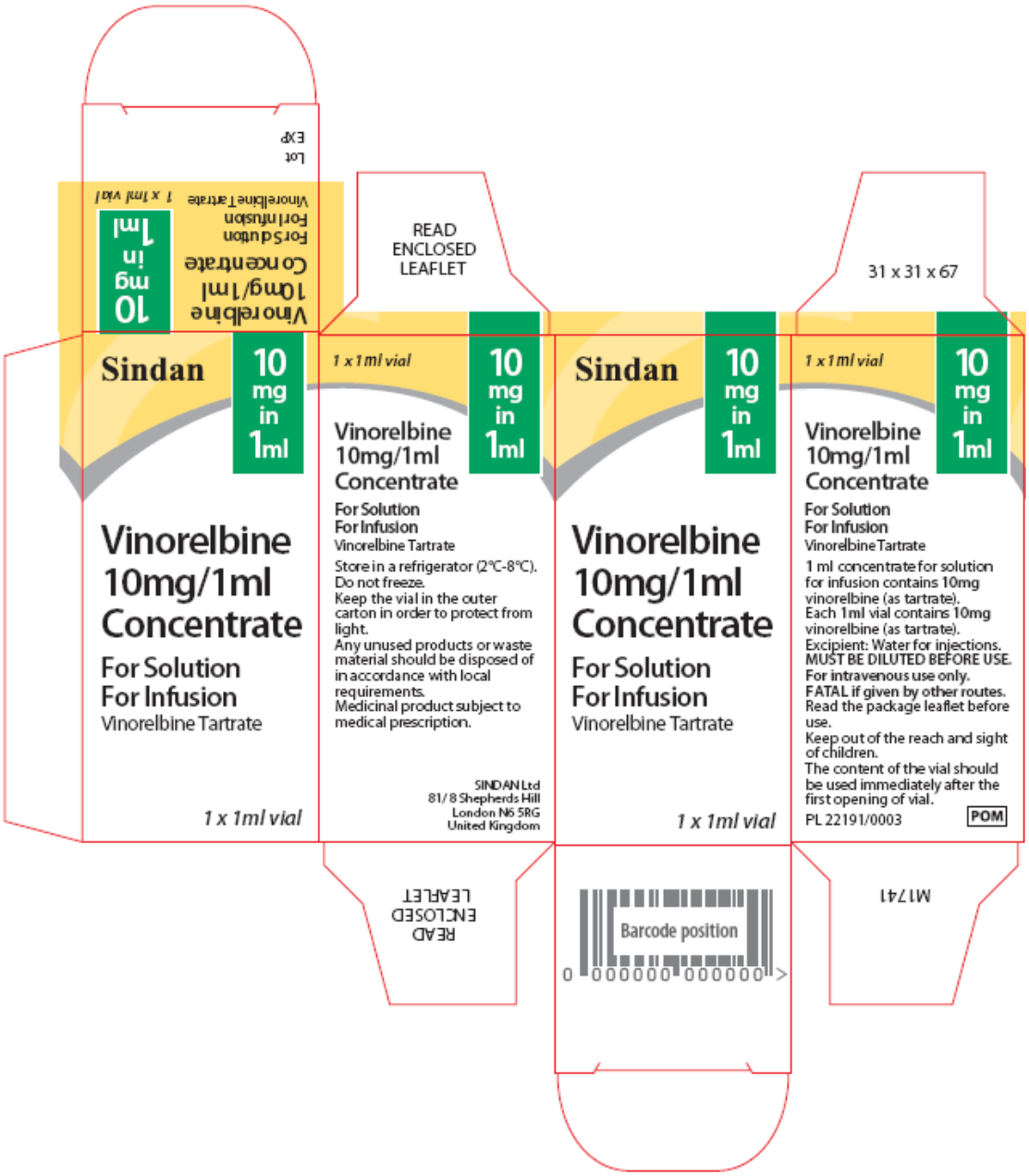
Vinorelbine 10 mg/ml concentrate for solution for infusion must be given strictly intravenously: it is very important to make sure that the cannula is accurately placed in the vein before starting to infuse the solution.
If the drug extravasates during intravenous administration, a substantial local 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.
Any unused product or waste material should be disposed of in accordance with local requirements.

Administration and Dosage
Strictly by intravenous injection through an infusion line: FATAL if given by other routes.
The use of intrathecal route is contra-indicated.
In adults:
-Vinorelbine 10 mg/ml concentrate for solution for infusion is usually given at 25-30mg/m^2 weekly.
-Vinorelbine 10 mg/ml concentrate for solution for infusion may be administered by slow bolus (5-10 minutes) after dilution in 20-50 ml of 0.9% Sodium Chloride solution or by a short infusion (20-30 minutes) after dilution in 125 ml of 0.9% Sodium Chloride solution. Administration should always be followed by a 0.9% Sodium Chloride infusion to flush the vein.

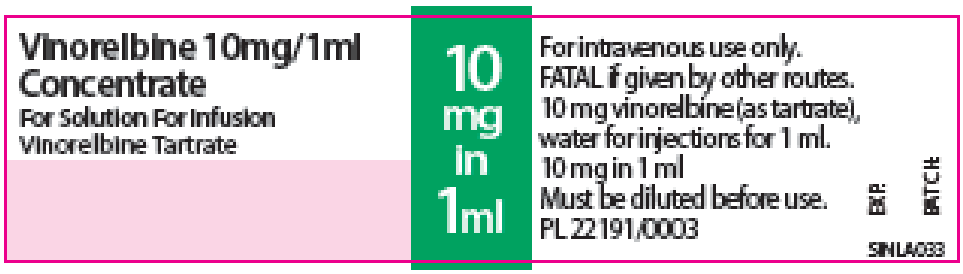
Dose modifications:
In patients with massive liver metastases (i.e. >75% of liver volume replaced by the tumour), it is empirically suggested that the dose be reduced by 1/3 and the haematological toxicity closely followed-up.
There is no pharmacokinetic rationale for reducing vinorelbine dose in patients with impaired kidney function.
The dose limiting toxicity of vinorelbine is mainly neutropenia. 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.
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.
The physicochemical and microbiological stability of the drug product after dilution in the recommended solutions for infusion has been demonstrated for 24 hours at 2-8°C. From the microbiological point of view, the product must be used immediately after dilution. Other in-use time periods and other in-use storage conditions are the responsibility of the user.
An expiry date is given on the outer carton and vial label of the product. It should not be used after this date.
Please refer to the SPC for further information.

LABELLING

PL 22191/0003 - Carton for 10mg / 1ml pack



Label



PL 22191/0004 - Carton for 50mg / 5ml pack

Label