VINORELBINE 10MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION
PL 33410/0041

UKPAR

TABLE OF CONTENTS

Lay Summary  Page 2
Scientific discussion  Page 3
Steps taken for assessment  Page 12
Steps taken after authorisation – summary  Page 13
Summary of Product Characteristics  Page 14
Patient Information Leaflet  Page 23
Labelling  Page 27
VINORELBINE 10MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION
PL 33410/0041

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency granted Apsla Limited a Marketing Authorisation (licence) for the medicinal product Vinorelbine 10mg/ml concentrate for solution for infusion (PL 33410/0041) on 9th September 2010. This is a prescription-only medicine (POM) for the treatment of cancer, specifically advanced non-small cell lung cancer and advanced breast cancer.

Vinorelbine 10mg/ml concentrate for solution for infusion contains the active ingredient vinorelbine tartrate, which causes cancer cells to die.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Vinorelbine 10mg/ml concentrate for solution for infusion outweigh the risks; hence a Marketing Authorisation has been granted.
## SCIENTIFIC DISCUSSION

### TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>4</td>
</tr>
<tr>
<td>Pharmaceutical assessment</td>
<td>5</td>
</tr>
<tr>
<td>Preclinical assessment</td>
<td>9</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>10</td>
</tr>
<tr>
<td>Overall conclusions and risk benefit assessment</td>
<td>11</td>
</tr>
</tbody>
</table>
INTRODUCTION

The UK granted a Marketing Authorisation for the medicinal product Vinorelbine 10mg/ml concentrate for solution for infusion (PL 33410/0041) to Apsla Limited on 9th September 2010. This product is a prescription-only medicine.

This application was submitted according to Article 10(1) of Directive 2001/83/EC. The application refers to the innovator product, Navelbine, 10mg/ml concentrate for solution for infusion, licensed to Pierre Fabre Limited, UK, on the 11th April 1989 (PL 00603/0028). The reference product has been authorised in the EEA for over 10 years.

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.

The pharmacovigilance system, as described by the MAH, fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well established.

No new pre-clinical or clinical studies were performed, which is acceptable given that the proposed product is a generic medicinal product of the reference product that have been licensed for over 10 years.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder (MAH) and it was, therefore, judged that the benefits of taking Vinorelbine 10mg/ml concentrate for solution for infusion outweigh the risks; hence a Marketing Authorisation has been granted.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Vinorelbine tartrate
INN: Vinorelbine tartrate

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

Structure

![Structure of Vinorelbine Tartrate](image)

Molecular mass: 1079
Molecular formula: C_{45}H_{54}N_{4}O_{8}.2C_{4}H_{6}O_{6}

General Properties

Description: White to almost white hygroscopic powder.

Solubility: Practically insoluble in hexane, freely soluble in methanol and in acetone.

Vinorelbine tartarate is the subject of a European Pharmacopoeia monograph (Ph Eur).

Manufacture

Synthesis of the drug substance from the designated starting materials 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.
An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. The primary packaging is amber bottles packed in a food grade transparent polythene bag and placed in a steel container along with silica gel sachets and Styrofoam chips. Suitable specifications and Certificates of Analysis have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging. Based on the data, a re-test period of 24 months has been set, when the active is stored in the proposed packaging at a temperature of -20°C to -10°C. This is satisfactory.

**MEDICINAL PRODUCT**

**Other ingredients**

The drug product is licensed in two vial sizes of 10mg/ml and 50mg/5ml, and is presented as a clear colourless concentrate for solution for infusion. Each vial contains 10mg of the active ingredient, vinorelbine tartrate, per ml of solution. Vinorelbine must be diluted prior to administration in a 50 ml volume of sodium chloride 9 mg/ml (0.9 %) solution for injection or in 5 % glucose solution for injection. Refer to section 4.2 and 6.6 of the SmPC for full details the method of administration and handling of the medicinal product.

Other ingredients consist of pharmaceutical excipients, namely water for injections, nitrogen gas and sodium hydroxide (for pH adjustment). Appropriate justification for the inclusion of each excipient has been provided. All excipients used comply with their relevant European Pharmacopoeia (Ph. Eur) monographs with the exception of nitrogen gas which is controlled to the National Formulary (NF). Satisfactory Certificates of Analysis have been provided for all excipients.

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 of the proposed product. None of the excipients are sourced from genetically modified organisms.

**Pharmaceutical Development**

Details of the pharmaceutical development of the medicinal products have been provided and are satisfactory. The aim of the pharmaceutical development was to obtain a medicinal product pharmaceutically and therapeutically equivalent to the innovator product, Navelbine 10mg/ml concentrate for solution for infusion (Pierre Fabre Ltd), using standard safe excipients.
Comparative impurity data were provided for the test and innovator products. The impurity profiles were comparable and satisfactory.

Compatibility studies have been carried with 0.9% saline and also 5% dextrose solution. Dilution studies show that the product is chemically stable in 0.9% saline and 5% dextrose up to 24 hours at 5°C to 30°C. This is acceptable.

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

In-process controls were considered appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are accepted.

**Finished Product Specification**
The finished product specifications are provided for both release and shelf-life and are 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. Satisfactory batch analysis data are provided for the 10mg and 50mg presentations. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

**Container Closure System**
The finished product is licensed for marketing in glass vials (Type I) of appropriate volume by a reformulated rubber stopper. The stopper is covered with a flip off tear off aluminium seal, externally lacquered with a colourless lacquer, with a red coloured disc. Each vial contains vinorelbine tartrate equivalent to 10mg vinorelbine.

The vials are packaged with the patient information leaflet into outer cardboard cartons. Vial sizes of 1ml and 5ml are available in packs of 1 vial.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for 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 2 years has been set for the unopened vial, which is satisfactory. Storage conditions are instructions are ‘Store in a refrigerator (2oC -8oC) and ‘Store in the original package in order to protect from light’.

Chemical and physical in-use stability of vinorelbine diluted in normal saline solution or dextrose solution has been demonstrated for 24 hours at 5°C - 30°C when stored in the polyvinylchloride (PVC) perfusion bags.

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 normally not be longer than 24 hours at 2 to 8°C, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.
Bioequivalence Study
Bioequivalence studies are not necessary to support this application for a parenteral product.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The approved SmPCs, PILs and labelling are pharmaceutically acceptable. Mock-ups of the package leaflet and labelling have been provided.

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

Expert Report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier. The CV of the expert has been provided.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.
**PRECLINICAL ASSESSMENT**

This application was submitted according to Article 10.1 of Directive 2001/83/EC, as amended.

The pharmacodynamic, pharmacokinetic and toxicological properties of vinorelbine tartrate are well-known. Therefore, no further studies are required and the applicant has provided none.

The pre-clinical overview was written by a suitably qualified person and is satisfactory. The *curriculum vitae* of the expert has been provided.

A suitable justification has been provided for the non-submission of an environmental risk assessment.
**CLINICAL ASSESSMENT**

**Pharmacokinetics**
No new data have been submitted and none are required for an application of this type.

Vinorelbine 10mg/ml concentrate for solution for infusion is a generic version of Navelbine, 10 mg / ml concentrate for solution for infusion, Pierre Fabre Ltd (PL 00603/0028). The use of the reference product is well-established in the UK. Both products contain the same quantitative and qualitative composition of the active ingredient, vinorelbine. Thus, in accordance with the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev.1/Corr), the applicant is not required to submit a bioequivalence study, if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product.

**Pharmacodynamics**
No new data have been submitted and none are required for an application of this type.

**Clinical efficacy**
No new data have been submitted and none are required for an application of this type.

**Clinical safety**
No new safety data have been submitted or required for this generic application. As vinorelbine is a well-known product with an acceptable adverse event profile, this is satisfactory.

**Expert Report**
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified physician. The *curriculum vitae* of the expert has been provided.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC and PIL are medically acceptable, and consistent with those for the reference product. The labelling is medically acceptable and in-line with current requirements.

**MAA form**
The MAA form is medically satisfactory.

**Conclusion**
There are no objections to approval of Vinorelbine 10mg/ml concentrate for solution for infusion from a clinical point of view.
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 has been demonstrated to be a generic version of the reference product Navelbine, 10 mg / ml concentrate for solution for infusion, Pierre Fabre Ltd., UK, licensed on the 11th April 1989 (PL 00603/0028).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The SmPC and PIL are acceptable, and consistent with those for the reference product. The labelling is acceptable and in-line with current requirements.

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

BENEFIT/RISK 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 Vinorelbine 10mg/ml concentrate for solution for infusion and the reference product Navelbine, 10 mg / ml concentrate for solution for infusion (Pierre Fabre Ltd., UK) are interchangeable. Extensive clinical experience with vinorelbine tartrate is considered to have demonstrated the therapeutic value of the active substance. The benefit:risk is, therefore, considered to be positive.
**STEPS TAKEN FOR ASSESSMENT**

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 23rd February 2009.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 11th March 2009.</td>
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<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 12th June 2009 and 16th June 2010.</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 6th January 2010 and 13th August 2010.</td>
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<tr>
<td>5</td>
<td>The application was determined on 9th September 2010.</td>
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# STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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VINORELBINE 10MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION
PL 33410/0033-36

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Vinorelbine 10mg/ml Concentrate for solution for infusion (PL 33410/0041) is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Vinorelbine 10 mg /ml Concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Vinorelbine 10 mg/ ml as Vinorelbine tartrate
Each 1ml vial of Vinorelbine 10 mg/ml concentrate for solution for infusion contains 13.85mg of Vinorelbine tartrate, which is equivalent to 10mg of Vinorelbine.
Each 5ml vial of Vinorelbine 50 mg/ 5ml concentrate for solution for infusion contains 69.25mg of Vinorelbine tartrate, which is equivalent to 50mg of Vinorelbine
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Concentrate for solution for infusion
Vinorelbine 10 mg/ ml Injection is a clear colourless solution in Type I  2 ml transparent flint glass vial with 13 mm reformulated rubber stoppers sealed with 13 mm aluminium flip-off tear-off seal.
Vinorelbine 50 mg/ 5ml Injection is a clear colourless solution in Type I  5 ml transparent flint glass vial with 20 mm reformulated rubber stoppers sealed with 20 mm aluminium flip-off tear-off seal

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
FOR INTRAVENOUS USE ONLY AFTER APPROPRIATE DILUTION.
The use of intrathecal route is contra-indicated: see section 4.4
Vinorelbine must only be administered by the intravenous route as an infusion over 5 – 10 minutes. Instructions for use and handling: see section 6.6.
Administration
-It is recommended to infuse Vinorelbine over 5 to 10 minutes after dilution in a 50 ml infusion bag with 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 a normal saline infusion to lush the vein.
- The infusion time of 5 to 10 minutes must be followed as the risk of venous irritation is increased if the infusion exposure time is increased.
- It is vital to ensure that the cannula is accurately placed in the vein before starting to infuse Vinorelbine. If the drug extravasates into the surrounding tissue during the administration considerable local irritation may occur. In this case, the administration should be stopped, the vein flushed with 0.9 % sodium chloride solution and the remaining dose administered in another vein. The management of any extravasation should be according to local hospital guidelines and policies.
In adults:
Vinorelbine is usually given at 25-30mg/m² weekly.
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.

**Administration in the elderly**

Clinical experience has not detected any significant differences among elderly patients with regard to the response rate, although greater sensitivity in some of these patients cannot be excluded. Age does not modify the pharmacokinetics of Vinorelbine: see section 5.2.

**Administration in patients with liver insufficiency**

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 20 mg/m² (see sections 4.4 and 5.2).

**Administration in patients with renal insufficiency:**

Given the minor renal excretion, there is no pharmacokinetic justification for reducing the dose of Vinorelbine in patients with renal insufficiency: see section 4.4.

**Administration in children**

Vinorelbine is not recommended for use in children due to a lack of data on safety and efficacy (see section 5.1).

### 4.3 Contraindications

- Known hypersensitivity to Vinorelbine or other vinca alkaloids, or to any of the excipients.
- Pregnancy (see section 4.6).
- Lactation (see section 4.6).
- In combination with yellow fever vaccine: see section 4.5
- Neutrophil count < 1500/mm³ or severe infection current or recent (within 2 weeks).
- Platelet count less than 75,000/mm³

### 4.4 Special warnings and precautions for use

**Special warnings**

Vinorelbine must only be administered by the intravenous route as an infusion over 5 – 10 minutes. The use of intrathecal route is contra-indicated.

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

The risk of venous irritation is increased if the infusion exposure time exceeds the recommendation time of 5 to 10 minutes.

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/mm³ and/or the platelet count is below 75000/ mm³ 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 for use**

Special care should be taken when prescribing for patients with history of ischemic heart disease: see section 4.8.

The pharmacokinetics of Vinorelbine is not modified in patients presenting moderate or severe liver impairment: see section 5.2.

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. see sections 4.2, 5.2

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

This product is specifically contra-indicated with yellow fever vaccine and its concomitant use with other live attenuated vaccines is not recommended.

Caution must be exercised when combining Vinorelbine and strong inhibitors or inducers of CYP3A4: see section 4.5, and its combination with phenytoin (like all cytotoxics) and with itraconazole (like all vinca alkaloids) is not recommended.
All contact with the eyes should be strictly avoided. There is a risk of severe irritation and even corneal ulceration if the drug is sprayed under pressure. Immediate washing of the eye with normal saline solution should be undertaken if any contact occurs.

4.5 Interaction with other medicinal products and other forms of interaction

Yellow fever vaccine: as with all cytotoxics, risk of fatal generalised vaccine disease: see section 4.3.

Concomitant use not recommended

Live attenuated vaccines: (for yellow fever vaccine, see concomitant use contraindicated) as with all cytotoxics, risk of generalised vaccine disease, possibly fatal. This risk is increased in patients already immunodepressed by their underlying disease. It is recommended to use an inactivated vaccine when one exists (e.g. poliomyelitis): see section 4.4

Phenytoin: as with all cytotoxics, risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic drug or risk of toxicity enhancement or loss of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin.

Itraconazole: as with all vinca-alkaloids, increased neurotoxicity of vinca-alkaloids due to the decrease of their hepatic metabolism

Concomitant use to take into consideration

Cisplatin: There is no mutual pharmacokinetic interaction when combining Vinorelbine with cisplatin over several cycles of treatment. However, the incidence of granulocytopenia associated with Vinorelbine use in combination with cisplatin is higher than associated with Vinorelbine single agent.

Mitomycin C: as with all vinca-alkaloids, increased risk of pulmonary toxicity Caution is advised when using Vinorelbine and mitomycin C simultaneously.

The combination of Vinorelbine with other drugs with known bone marrow toxicity is likely to exacerbate the myelosuppressive adverse effects.

As CYP 3A4 is mainly involved in the metabolism of Vinorelbine, combination with strong inhibitors of this isoenzyme (e.g. azole antifungals such as ketoconazole and itraconazole) could increase blood concentrations of Vinorelbine and combination with strong inducers of this isoenzyme (e.g. rifampicin, phenytoin) could decrease blood concentrations of Vinorelbine.

Anticoagulant treatment: as with all cytotoxics, the frequency of INR (International Normalised Ratio) monitoring should be increased due to the potential interaction with oral anticoagulants and increased variability of coagulation in patients with cancer.

4.6 Pregnancy and lactation

- 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).
- In case of a vital indication for treatment with Vinorelbine during pregnancy a medical consultation concerning the risk of harmful effects for the child should be conducted. 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).

Lactation

It is unknown whether Vinorelbine is excreted in human breast milk. The excretion of Vinorelbine in milk has not been studied in animal studies.

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

Fertility

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

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 the MedDRA frequency. Additional Adverse reactions from Post Marketing experience has been added according to the MedDRA classification with the frequency Not known.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Descriptions</th>
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<tbody>
<tr>
<td>Very common</td>
<td>&gt;1/10</td>
</tr>
<tr>
<td>Common</td>
<td>&gt;1/100, &lt;1/10</td>
</tr>
<tr>
<td>Uncommon</td>
<td>&gt;1/1,000, &lt;1/100</td>
</tr>
<tr>
<td>Rare</td>
<td>&gt;1/10,000, &lt;1/1,000</td>
</tr>
<tr>
<td>Very rare</td>
<td>&lt;1/10,000, including isolated reports</td>
</tr>
<tr>
<td>Not known</td>
<td>Post marketing reports</td>
</tr>
</tbody>
</table>

See table of adverse reactions

The most commonly reported adverse drug reactions are bone marrow depression with neutropenia, leucopenia and anaemia, neurologic disorders, gastrointestinal toxicity with nausea, vomiting, stomatitis and constipation, transient elevations of liver function tests, alopecia and local phlebitis.

Infections and infestations:
- **Common**: Infection bacterial, viral or fungal at different sites.
- **Uncommon**: Septicaemia [very rarely fatal].
- **Not known**: Neutropenic sepsis, sometimes 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.
  - Leucopenia
  - Anaemia
- **Common**: Thrombocytopenia.
- **Not known**: Febrile neutropenia

Immune system disorders:
- **Not known**: Systemic allergic reactions as anaphylaxis, anaphylactic shock or anaphylactoid type reaction.

Endocrine disorders:
- **Not known**: Inappropriate antidiuretic hormone secretion (SIADH)

Metabolism and nutrition disorders:
- **Rare**: Severe hyponatraemia
- **Not known**: Anorexia

Nervous system disorders:
- **Very 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
- Constipation
**Common:** 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:
**Very common:** Alopecia, usually mild in nature, may occur
**Rare:** Generalized cutaneous reactions

Musculoskeletal and connective tissue disorders:
**Common:** Arthralgia including jaw pain and myalgia.

General disorders and administration site conditions:
**Very common:** Reactions at the injection site may include erythema, burning pain, vein discoloration and local phlebitis
**Common:** Fatigue, fever, pain at different sites including chest pain and pain at the tumour site.
**Rare:** Local necrosis has been observed. Proper positioning of the cannula in the vein before starting to infuse Vinorelbine followed by liberal flushing of the vein can limit these effects

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Organ System</th>
<th>Very Common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/100)</th>
<th>Very rare(&lt;1/10,000), not known (cannot be estimated from the available data)</th>
<th>Not known</th>
</tr>
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<tbody>
<tr>
<td>Infections and infestation s</td>
<td>Infection bacterial, viral or fungal</td>
<td>Severe sepsis with other visceral failure. Septicaemia</td>
<td>Septicaemia complicated, Septicaemia fatal</td>
<td>Febrile neutropenia</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Bone marrow, Depression, Neutropenia, anaemia,</td>
<td>Thrombocytopenia</td>
<td></td>
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<tr>
<td>Immune system disorders</td>
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<td></td>
<td>Systemic allergic reactions</td>
</tr>
<tr>
<td>Endocrine disorders</td>
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<td></td>
<td></td>
<td>Inappropriate anti diuretic hormone secretion (SIADH)</td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Anorexia</td>
</tr>
<tr>
<td>Disorders</td>
<td>Neurologic disorders</td>
<td>Severe Paresthesias</td>
<td>Ischemic heart disease, Angina pectoris, Myocardial infarction</td>
<td>Tachycardia, Palpitations, Heart rhythm disorders</td>
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<tr>
<td>Nervous system disorders</td>
<td>Weakness of the lower extremities</td>
<td></td>
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<tr>
<td>Cardiac disorders</td>
<td></td>
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</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypotension, Hypertension, Flushing, Peripheral coldness.</td>
<td>Severe hypotension, Collapse.</td>
<td></td>
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</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnoea, Bronchospasm</td>
<td>Interstitial pneumopathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Stomatitis, Nausea, Vomiting, Constipation</td>
<td>Diarrhoea</td>
<td>Paralytic ileus, pancreatitis</td>
<td></td>
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<tr>
<td>Hepatic disorders</td>
<td>Transient elevations of liver function tests</td>
<td></td>
<td></td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia</td>
<td>Generalized cutaneous reactions</td>
<td></td>
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</tr>
<tr>
<td>Musculoskeletal, connective tissue disorders</td>
<td>Arthralgia including jaw pain and myalgia.</td>
<td></td>
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</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Reactions at injection site as: Erythema, Burning pain, Vein discoloration, Local phlebitis</td>
<td>Fatigue, Fever, Pain at different sites, chest pain and pain at tumour site, Local necrosis</td>
<td></td>
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</tr>
</tbody>
</table>
4.9 Overdose

Symptoms
Overdosage with Vinorelbine could produce bone marrow hypoplasia sometimes associated with infec-
tion, fever and paralytic ileus.

Emergency procedure
General supportive measures together with blood transfusion and broad spectrum antibiotic therapy
should be instituted as deemed necessary by the physician.

Antidote
There is no known antidote for overdosage of Vinorelbine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Vinca alkaloids and analogues
ATC Code: L01CA04
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. :
see section 4.2.

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%). However, Vinorelbine binds strongly to blood cells and especially to platelets 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
All metabolites of Vinorelbine are formed by CYP 3A4 isoform of cytochromes P450, except 4-O-
deacetylVinorelbine likely to be formed by carboxylesterases. 4-O-deacetylVinorelbine is the only
active metabolite and the main one observed in blood.
Neither sulphonic or glucuronic conjugates are found.
Elimination
The mean terminal half-life of Vinorelbine is around 40 hours. 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 metabolites.

Special patient groups
Renal impairment
The effects of renal dysfunction on the pharmacokinetic of Vinorelbine have not been studied.
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 is 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/m².

Elderly patients

A Study with Vinorelbine in elderly patients (70 years) with NSCLC demonstrated that pharmacokinetics of Vinorelbine were not influenced by age. However, since elderly patients are frail, caution should be exercised when increasing the dose of Vinorelbine: see section 4.2.

**Pharmacokinetic / pharmacodynamic relationships.**

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 polyplody. It is therefore to be assumed that Vinorelbine can also cause mutagenic effects (induction of aneuploidy) in man.

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

**Reproductive toxicity**

In animal reproductive studies Vinorelbine was embryo- and feto-lethal and teratogenic. The NOEL in the rat was 0.26 mg/kg every 3 days. Following peri/postnatal administration in the rat at doses of 1.0 mg/kg every 3 days i.v., retarded weight gain was found in the offspring up to the 7th week of life.

**Safety pharmacology**

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

Haemodynamic and electrocardiographic studies on animals have been carried out; 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

<table>
<thead>
<tr>
<th>EXCIPIENTS</th>
<th>FORMULATION</th>
<th>10 mg/ 1 ml</th>
<th>50 mg/ 5 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water for injections (ml) qs</td>
<td>1.00</td>
<td>5.00</td>
<td></td>
</tr>
<tr>
<td>Sodium hydroxide qs</td>
<td>for pH adjustment</td>
<td>For pH adjustment</td>
<td></td>
</tr>
<tr>
<td>Nitrogen qs</td>
<td>Inert filling</td>
<td>Inert filling</td>
<td></td>
</tr>
</tbody>
</table>

#### 6.2 Incompatibilities

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

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

#### 6.3 Shelf life

The product is stable for 2 years.

Chemical and physical in-use stability of Vinorelbine diluted in normal saline solution or dextrose solution has been demonstrated for 24 hours at 5°C - 30°C when stored in the PVC perfusion bags.
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 normally not be longer than 24 hours at 2 to 8°C, unless reconstitution / dilution (etc) has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
Store in a refrigerator (2°C - 8°C).
Store in the original package in order to protect from light.
For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container
Vinorelbine is distributed in moulded glass vials (Type I) of appropriated volume closed by a reformulated rubber stopper. The stopper is covered with a flip off tear off aluminium seal externally lacquered by colourless lacquer, with red coloured disc.
Vials sizes of 1ml and 5 ml, are available in packs of 1 vial.

6.6 Special precautions for disposal
Handling and Use:
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.
- Caution should be exercised in handling and preparing the Vinorelbine solution:
- Suitable eye protection, disposable gloves, face mask and disposable apron should be worn.
- 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.

Preparation of the solution for infusion
Vinorelbine must be diluted prior to administration in a 50 ml volume of sodium chloride 9 mg/ml (0.9 %) solution for injection or in 5 % glucose solution for injection.
In case of polychemotherapy, Vinorelbine should not be mixed with other agents
There is no content / container incompatibility between Vinorelbine and transparent glass bottle, PVC bag, or infusion set with PVC tubing.
The intra-thecal route is contraindicated: see sections 4.2 and 4.4
Vinorelbine must only be administered by the intravenous route as an infusion.
For further instructions on administration: see section 4.2.

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

7 MARKETING AUTHORISATION HOLDER
APSLA Limited,
Bayview House,
49 North Strand Road,
Dublin 3, Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 33410/0041

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
09/09/2010

10 DATE OF REVISION OF THE TEXT
09/09/2010
PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

VINORELBINE 10mg/ml Concentrate for solution for infusion

VINORELBINE (as tartrate)

(10mg in 1ml & 50mg in 5ml)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor 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 get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What VINORELBINE is and what it is used for
2. Before you use VINORELBINE
3. Possible side effects
4. How to store VINORELBINE
5. Further information

1. WHAT VINORELBINE IS AND WHAT IT IS USED FOR

The name of your drug is VINORELBINE 10mg/ml Concentrate for solution for infusion. In the rest of this leaflet your medicine is called VINORELBINE.
VINORELBINE is one of a group of drugs called the vinca alkaloids.
VINORELBINE is intended for the treatment of cancer, specifically advanced non small cell lung cancer and advanced breast cancer that has not responded to other medicines.
It is not recommended for use by children under 18 years old.

2. BEFORE YOU USE VINORELBINE

Do not use VINORELBINE:
- if you are pregnant or think that you might be pregnant
- if you are breast-feeding
- if you are allergic (hypersensitive) to the active substance (VINORELBINE), or to any of the related family of cancer drugs called the vinca alkaloids
- if you have a low white blood cell (leucopenia) count or a severe infection
- if you have a low blood or platelet count (thrombocytopenia)
- if you plan to receive a yellow fever vaccination or have just received one.

Take special care with VINORELBINE

Please inform your doctor if:
- you have a history of heart attack or severe chest pain
- you have problems with your liver or have received radiotherapy where the treatment field included the liver
- you have signs or symptoms of infections (such as fever, chills, joint pain)
- you take or have recently taken any other medicines including medicines obtained without a prescription.
- you plan to have a vaccination or have just had one.

Before and during your treatment with VINORELBINE, blood cell counts are performed to check that it is safe for you to receive treatment.
If the results of any analysis are not satisfactory, your treatment may be delayed and further checks made until these values return to normal.

Using with other medicines:

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

Your doctor should take special attention if you are taking the following medicines:
- medicines used to thin your blood (anticoagulants)
- an anti-epilepsy medicine called phenytoin
- an anti-fungal medicine called itraconazole and ketoconazole
- an anti-cancer medicine called mitomycin C
- medicines that impair your immune system such as ciclosporin and tacrolimus

Live attenuated vaccines (e.g. Measles vaccine, Mumps vaccine, Rabies vaccine) and yellow fever vaccines are not recommended with VINORELBINE as they may increase the risk of life-threatening vaccine disease.

If you are given VINORELBINE as well as medicines that affect your bone marrow it may make some of the side effects worse.

Using VINORELBINE with food and drink:

There are no known interactions with food and drink when using VINORELBINE. However, you should check with your doctor if taking alcohol is advisable for you.

Male fertility:

Men being treated with VINORELBINE are advised not to father a child during treatment and for up to 3 months after the end of the treatment.
The effects of anti-cancer drugs on the unborn child are not fully known. VINORELBINE is one of the anti-cancer drugs which are known to have adverse effects in pregnant animals.

Women of child-bearing potential:

Women of child-bearing potential must use effective contraception (birth control) during treatment and for up to 3 months after the end of the treatment.

Pregnancy and breast-feeding:

Pregnancy:
- Do not take VINORELBINE if you are pregnant or think that you might be pregnant.
- If you have to start treatment with VINORELBINE and are pregnant or if pregnancy occurs during your treatment with VINORELBINE, you must immediately contact your doctor for advice.

Breast-feeding:
- Do not take VINORELBINE if you are breast-feeding.
- Breast-feeding must be discontinued if treatment with VINORELBINE is necessary.

Driving and using machines:

No studies on the effects on the ability to drive and use machines have been performed. However, some of the possible side effects of VINORELBINE could affect your ability to drive or perform skilled tasks. See section 4. Possible side effects below for details. Therefore, it is recommended that you should not drive if you feel unwell or if your doctor has advised you not to drive.
3. HOW TO USE VINORELBINE

VINORELBINE should be prescribed by a qualified doctor who is experienced in the use of cancer treatments. VINORELBINE is used in patients over 18 years old. It is not recommended for use by children under 18 years old.

Dosage

Before and during treatment with VINORELBINE your doctor will check your blood cell count. The results of your blood test will decide when you receive your treatment. The dose will depend on your height and weight and your general condition. Your doctor will calculate your body surface area and will determine the dose you should receive.

Frequency of administration

Normally VINORELBINE is scheduled once a week. The frequency will be determined by your doctor who will take into account any other medicines you are being given.

Duration of treatment

The duration of your treatment is decided by your doctor.

Method and route of administration

- VINORELBINE must be injected into your veins. It will be given by an infusion into one of your veins. It will take between 5 to 10 minutes.
- After administration the vein will be rinsed thoroughly with a sterile solution.

If you use more VINORELBINE than you should

Your dose of VINORELBINE is carefully monitored and checked by your doctor and pharmacist. However, although you will have received the correct amount of chemotherapy your body may sometimes react giving severe symptoms. Some of these symptoms may develop as signs of an infection (e.g. fever, chills, joint pain). You may also become severely constipated. You must immediately contact your doctor if any of these severe symptoms occur.

If you stop using VINORELBINE

Your doctor will decide when you should stop your treatment. However, if you want to stop your treatment earlier, you should discuss other options with your doctor.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, VINORELBINE can cause side effects, although not everybody gets them.

While taking VINORELBINE if you develop any of the following symptoms you should contact your doctor immediately:

- signs of a major infection such as cough, fever, chills, etc.
- severe headaches or dizziness when you stand up
- severe chest pain which is not normal for you
- signs of allergy such as itching, shortness of breath

Below is a list of side effects that have occurred in some people following treatment with VINORELBINE. This list is classified according to the decreasing frequency of side effects occurrence.

<table>
<thead>
<tr>
<th>Very common side effects (can occur in more than 1 in 10 patients treated)</th>
<th>What should you do?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling sick (nausea)</td>
<td>Immediately contact your doctor if this becomes uncontrollable. These side effects may be controlled with standard anti-nausea therapy.</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>A fall in white blood cells which makes you more vulnerable to infection. This can commonly cause bacterial, viral or fungal infections in your body (respiratory, urinary, gastro-intestinal systems and possibly others).</td>
<td>Immediately contact your doctor, especially if your temperature reaches 38°C or higher.</td>
</tr>
<tr>
<td>A fall in red blood cells (anemia) which can make the skin pale and cause weakness or breathlessness</td>
<td>Immediately contact your doctor for treatment, these symptoms become severe.</td>
</tr>
</tbody>
</table>

INFORMATION FOR HEALTHCARE PROFESSIONALS

The following information is intended for medical and healthcare professionals only.

Below is a summary of information to assist in the preparation and administration of VINORELBINE 10 mg/ml concentrate for solution for infusion.

The preparation and administration of VINORELBINE should be carried out by trained staff and as with all cytotoxic agents, precautions should be taken to avoid exposing staff during pregnancy.

Handling:

Procedures for proper handling and disposal of cytotoxic drugs should be considered.

As with other cytotoxic compounds, caution should be exercised in handling and preparing the VINORELBINE solution:

- Suitable eye protection, disposable gloves, face mask and disposable apron should be worn.
- Avoiding spills or leakage should be carefully observed. Immediate immediate washing of the eye with sodium chloride 9 mg/ml (0.9%) solution for injection should be undertaken if any contact occurs.
- On completion, any exposed surface should be thoroughly cleaned and hands and face washed.

Preparation of the solution for infusion:

VINORELBINE must be diluted prior to administration in a 50 ml infusion bag with sodium chloride 9 mg/ml (0.9%) solution for injection or in 5% glucose solution for injection.

VINORELBINE should not be diluted in alkaline solutions as there is a risk of precipitation.

After dilution VINORELBINE in sodium chloride 9 mg/ml (0.9%) solution for injection or in glucose solution for injection 5%, Chemical and Physical stability of VINORELBINE diluted in normal saline solution or dextrose solution has been demonstrated for 24 hours at 3°C - 10°C or in the refrigerator (2°C - 8°C) when stored in the PVC infusion bags.

MHRA-UKPAR – Vinorelbine 10mg/ml concentrate for solution for infusion PL 33410/0041
<table>
<thead>
<tr>
<th>Common side effects (can occur in less than 1 in 10 patients treated)</th>
<th>What should you do?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of some reflex reactions, occasionally difference in the perception of touch (Wheals) of the lower extremities</td>
<td>Immediately contact your doctor for treatment, should these symptoms become severe.</td>
</tr>
<tr>
<td>Inflammation or sore in the mouth or throat ( stomatitis)</td>
<td>Immediately contact your doctor.</td>
</tr>
<tr>
<td>Constipation. If you have abdominal pain or if you do not have a bowel movement for several days</td>
<td></td>
</tr>
<tr>
<td>Abnormal liver test</td>
<td>Your doctor should check your liver function when you are receiving chemotherapy.</td>
</tr>
<tr>
<td>Hair loss (alopecia)</td>
<td>Ask your doctor for advice if the symptoms persist. These are possible symptoms when receiving chemotherapy.</td>
</tr>
<tr>
<td>Rash: at the site where Vinorelbine was administered as such as</td>
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<tr>
<td>Redness (erythema)</td>
<td></td>
</tr>
<tr>
<td>swelling (edema)</td>
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<tr>
<td>Vein discomfort</td>
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<tr>
<td>inflammation of the veins (local phlebitis)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Uncommon side effects (can occur in less than 1 in 100 patients treated)</th>
<th>What should you do?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiredness</td>
<td>If these symptoms become severe, immediately contact your doctor.</td>
</tr>
<tr>
<td>Fever</td>
<td></td>
</tr>
<tr>
<td>Pain at different sites in your body such as chest pain and pain where the transfusion is given.</td>
<td></td>
</tr>
<tr>
<td>A fall in platelets which increases the risk of bleeding or bruising (thrombocytopenia)</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
</tr>
<tr>
<td>Joint pains (arthralgia)</td>
<td></td>
</tr>
<tr>
<td>Joint pain</td>
<td></td>
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<tr>
<td>Muscle pain (myalgia)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rare side effects (can occur in less than 1 in 1,000 patients treated)</th>
<th>What should you do?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effects on your blood:</td>
<td></td>
</tr>
<tr>
<td>Serious signs of a major infection such as cough, fever, chills and blood infection.</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td></td>
</tr>
<tr>
<td>Diaphoresis</td>
<td></td>
</tr>
<tr>
<td>Dyspnoea (breathing difficulties)</td>
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</tr>
<tr>
<td>Dizziness (vertigo)</td>
<td></td>
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<tr>
<td>Palpitations</td>
<td></td>
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<tr>
<td>Hypotension (low blood pressure)</td>
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<tr>
<td>Hyporadial</td>
<td></td>
</tr>
<tr>
<td>Shock</td>
<td></td>
</tr>
<tr>
<td>Effects on your heart and blood vessels:</td>
<td></td>
</tr>
<tr>
<td>Reduced blood pressure (hypotension) with symptoms such as dizziness or fainting</td>
<td></td>
</tr>
<tr>
<td>Raised blood pressure (hypertension) with symptoms such as a headache, feeling tight in the hands and feet (peripheral oedema)</td>
<td></td>
</tr>
<tr>
<td>Effects on your respiratory system:</td>
<td></td>
</tr>
<tr>
<td>Difficulty in breathing or wheezing (dyspnoea and bronchoospasm)</td>
<td></td>
</tr>
<tr>
<td>Effects on your nervous system:</td>
<td></td>
</tr>
<tr>
<td>Severe difficulty with your body movements and sense of touch (serious paresthesias)</td>
<td></td>
</tr>
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<table>
<thead>
<tr>
<th>Very rare side effects (can occur in less than 1 in 10,000 patients treated)</th>
<th>What should you do?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irregular heart beats (tachycardia, palpitations) and heart rhythm disorder.</td>
<td>Immediately contact your doctor if you experience any of these side effects.</td>
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<tr>
<td>Life threatening infections in your body such as severe fever, chest infections and infections at other sites in your body (sepsis).</td>
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</tbody>
</table>

Other side effects have been reported: |
- Generalized allergic reactions. These are serious reactions which can cause severe difficulty in breathing, dizziness, rash affecting your whole body, swelling of the eyes and face, tingling (anaphylactic shock, angioedema, anaphylactoid reactions). |
- Low sodium levels due to an overproduction of a hormone causing fluid retention and resulting in swelling, tenderness or oedema. |
- Loss of appetite (anorexia). |

Do not be alarmed by this list. If you suffer from any of these side effects, or if you have any other unusual symptom or feeling, you should contact your doctor at once as possible. |

If any of the side effects get worse, or if you notice any side effects not listed in this booklet, please tell your doctor or pharmacist.
5. HOW TO STORE VINORELBINE

Keep out of the reach and sight of children.

Your medication should not be used after the expiry date which is stated on the container. The expiry date refers to the last day of that month.

Your medication should be stored in a refrigerator (2°C-8°C) and in the original package in order to protect from light.

After dilution, chemical and physical stability of VINORELBINE diluted in normal saline or dextrose solution has been demonstrated for 24 hours at 5°C-10°C in PVC infusion bags.

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°C-8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.

Any unused solution should be discarded immediately after use.

6. FURTHER INFORMATION

What Vinorelbine contains:
- The active ingredient is Vinorelbine (as tartrate).
- Each 10 mg/ml Vinorelbine Concentrate for solution for infusion contains 13.85 mg/ml of vinorelbine tartrate, which is equivalent to 10 mg/ml of Vinorelbine.
- Each 50 mg/ml Vinorelbine Concentrate for solution for infusion contains 69.25 mg/ml of vinorelbine tartrate, which is equivalent to 10 mg/ml of Vinorelbine.
- The other ingredients are water for injections, sodium hydroxide (for pH adjustment) and nitroglycerin gas (inert filling).

This leaflet does not contain the complete information on Vinorelbine. If you have any questions, or are not sure about anything, ask your doctor or pharmacist.

What Vinorelbine looks like and contents of the pack:
VINORELBINE 10 mg/ml Concentrate for solution for infusion is a clear colourless solution in Type I 2 ml transparent moulded glass vial with 15 mm reformulated rubber stoppers sealed with aluminium flip-off tear-off seal, with red coloured disc. It is available in pack size of 1 vial.
VINORELBINE 50 mg/ml Concentrate for solution for infusion is a clear colourless solution in Type I 5 ml transparent moulded glass vial with 30 mm reformulated rubber stoppers sealed with 50 mm aluminium flip-off tear-off seal, with red coloured disc. It is available in pack size of 1 vial.

Marketing Authorization Holder:
Apsia Limited, Bayview House, 49 North Strand Road, Dublin 3, Ireland.

Manufacturer:
Apsia Limited, Wakefield, West Yorkshire, WF1 4QX, England.

Marketing and Distributed By:
Apsia Pharmaceuticals Ltd., 9th Floor, CP House, 37-107 Upper Brook Road, Ealing, London W5 5TL.

This leaflet was revised in March 2010.

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°C-8°C, unless reconstitution / dilution (etc) has taken place in controlled and validated aseptic conditions.

Dosage and instructions for use:

FOR INTRAVENOUS USE ONLY AFTER APPROPRIATE DILUTION:
VINORELBINE must be administered by the intravenous route as an infusion.

The use of intravenous route is contraindicated:

It is recommended to infuse VINORELBINE over 5-10 minutes after dilution in a 50 ml infusion bag with sodium chloride 9 mg/ml (0.9%) solution for injection or in 5% glucose solution for injection.

After administration, the veins should be thoroughly flushed with at least 250 ml of isotonic solution.

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 into the surrounding tissue during the administration considerable local irritation may occur. In this case, the administration should be stopped, the vein flushed with normal saline solution and the remaining dose administered in another vein.

Do not infuse concurrently with another cytotoxic agent. It should be given as the first drug where the patient is treated with combination chemotherapy due to the risk of venous irritation.

Storage & Disposal:
Unopened vials should be stored in a refrigerator at a temperature of 2°C - 8°C in the original package in order to protect from light.

- The product should not be frozen as this could adversely affect the product.
- An expiry date is stated on both the vial and outer box and refers to the last day of that month.
- Do not use the product after this date.

VINORELBINE will be diluted and stored by hospital staff. Any unused product or waste should be disposed of in accordance with local requirements for cytotoxic drugs.
VINORELBINE 10MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION
PL 33410/0041

Read the package leaflet before use.
For single use only.

Following children, 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°C - 8°C, unless opening and dilution have taken place in controlled and validated aseptic conditions.

Discard any unused solution immediately after use.

Waste material may be disposed of by incineration.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

Pl. Holder:
APLTA Limited,
Bayview House, 49 North Strand Road, Dublin 3,
Ireland

Marketed and Distributed By:
APC Pharmaceuticals & Chemicals (Europe) Ltd.,
Suite 509, Park House, 111, Uxbridge Road, Ealing,
London W5 3LB
PL 33410/0041

Vinorelbine 10 mg/ml
Concentrate for solution for infusion
[10 mg in 1 ml]

Contains 10 mg Vinorelbine (as tartrate) in 1 ml of solution.
Also contains water for injections, sodium hydroxide (for pH adjustment), nitrogen gas (mass filling).

For intravenous use only.
Defit if given by other routes.
Must be diluted before use.
Store in a refrigerator.
Store in the original package in order to protect from light.

xxxxx

EXP:
Lot: