Public Assessment Report

Decentralised

Vinorelbine 10mg/ml concentrate for solution for infusion
Vinorelbine 50mg/5ml concentrate for solution for infusion

UK/H/1551/01/DC
UK/H/1551/02/DC

Pharmaceutical Works Polpharma S.A.
Lay Summary

The MHRA granted market authorisations for the medicinal products Vinorelbine 10mg/ml concentrate for solution for infusion (PL 25124/0014) and Vinorelbine 150mg/5ml concentrate for solution for infusion (PL 25124/0015) to Pharmaceutical Works Polpharma SA on 11/05/2009.

The drug products were demonstrated to be generic medical products of the reference product Navelbine® 10 mg/ml concentrate for solution for infusion by Pierre Fabre Medicament, registered in France since 11th April 1989. The products are prescription only medicines.

The active substance vinorelbine tartrate is a vinca alkaloid with a broad spectrum of anti-tumour activity. Vinorelbine is licensed in EU for the treatment of stage 3 and 4 non-small cell lung cancer (NSCLC) and the treatment of advanced breast cancer relapsing after or refractory to an anthracycline containing regimen.
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## Module 1

| **Product Name** | Vinorelbine 10mg/ml concentrate for solution for infusion  
Vinorelbine 50mg/5ml concentrate for solution for infusion |
<table>
<thead>
<tr>
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<tr>
<td><strong>Type of Application</strong></td>
<td>Complex Abridged Decentralised (Article 10.1)</td>
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<tr>
<td><strong>Active Substance (INN)</strong></td>
<td>Vinorelbine</td>
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<td><strong>Pharmacotherapeutic Classification (ATC)</strong></td>
<td>L01CA, vinca alkaloids and analogues</td>
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<td><strong>Pharmaceutical Form and Strength</strong></td>
<td>Concentrate for solution for infusion, 10mg/ml and 50mg/5ml</td>
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<td><strong>Procedure Numbers</strong></td>
<td>UK/H/1151/01-02/DC</td>
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<td><strong>RMS</strong></td>
<td>UK</td>
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<td><strong>CMS</strong></td>
<td>BG, CZ, PL, SK, HU, LT, LV, EE and RO</td>
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<tr>
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<td>05/03/2008</td>
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<td><strong>End Date</strong></td>
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<tr>
<td><strong>MA Number</strong></td>
<td>PL 25124/0014-5</td>
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</table>
| **Name and address of MA holder** | Pharmaceuticals Works Polpharma SA  
19 Pelplińska Street, Starogard Gdański  
83-200 Poland |
Module 2

Summary of Product Characteristics

SUMMARY OF PRODUCT CHARACTERISTICS

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 1 ml vial contains a total content of vinorelbine (as tartrate) of 10 mg
Each ml contains 10 mg of vinorelbine (as tartrate).
For excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Concentrate for solution for infusion
Clear, colourless solution with a pH of 3.3 to 3.8 and an osmolarity 47 mOsm/kg.

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 infusion only.
Vinorelbine 10 mg/ml concentrate for solution for infusion should be given in cooperation with a physician with extensive experience in therapy with cytostatics.
The use of intrathecal route is contra-indicated.

For instructions on dilution of the product before administration, see section 6.6.

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 normal saline or glucose 50 mg/ml (5%) solution or by a short infusion (20-30 minutes) after dilution in 125 ml of normal saline or glucose 50 mg/ml (5%) solution. Administration should always be followed with at least 250 ml of an isotonic solution to flush the vein.

Non-small cell lung cancer
As a single agent the normal dose is 25-30 mg/m², administered once weekly. In polychemotherapy the schedule regimen is a function of the protocol. The normal dose could
be used (25-30 mg/m²), but the frequency of the administration be reduced to for example day 1 and 5 every third week or day 1 and 8 every third week according to the regimen.

**Advanced or metastatic breast cancer**

The normal dose is 25-30 mg/m², administered once weekly.

The maximum tolerated dose per administration: 35.4 mg/m² body surface area.

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

For patients with severely reduced hepatic function caution and careful monitoring of haematological parameters is recommended. The dose may have to be reduced (see sections 4.4 and 5.2).

In patients with reduced kidney function, the dose does not have to be adjusted (see section 5.2).

Elderly: No dose reduction is required.

### 4.3 Contraindications

The use of intrathecal route is contraindicated.

Hypersensitivity to vinorelbine or other Vinca alkaloids.

Neutrophil granulocytes < 1.5 x 10⁹/l or serious, current or recent infection (within 2 weeks).

Platelet count below 7.5 x 10¹⁰/l.

Pregnancy.

Breast-feeding should be discontinued during treatment with vinorelbine (see section 4.6).

Severe hepatic impairment not related to the tumoral process.

Women of childbearing potential not using effective contraception (see sections 4.4 and 4.6).

In combination with yellow fever vaccine (see section 4.5).

### 4.4 Special warnings and precautions for use

Strictly for intravenous use only.

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

Close haematological monitoring should be performed during treatment (determination of haemoglobin level and number of leucocytes, neutrophils and platelets before each new infusion), since inhibition of the haematopoietic system is the main risk during treatment with vinorelbine.

- Neutropenia, which is non-cumulative and has its nadir between day 7 and 14 after administration, and is quickly reversible within 5-7 days, is the main dose-limiting adverse reaction. If the number of neutrophil granulocytes is below 1.5 x 10⁹/l and/or the platelet count is below 7.5 x 10¹⁰/l, the treatment should be postponed until recovery.

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

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

- The clinical relevance of impaired drug elimination capacity of the liver has not been characterised. Therefore no exact dose recommendation could be given. However in the pharmacokinetic study the highest administered dose in patients with severe liver dysfunction was 20 mg/m² (see section 5.2). For patients with severe hepatic impairment caution is recommended and careful monitoring of haematological parameters is required. Dosage reduction may also be required (see sections 4.2 and 4.3).
Vinorelbine 10 mg/ml concentrate for solution for infusion should not be given concomitantly with radiotherapy if the treatment field includes the liver.

- Vinorelbine 10 mg/ml concentrate for solution for infusion must not get into contact with the eye; risk of severe irritation and even corneal ulceration if the drug is sprayed under pressure. If this occurs, immediately rinse the eye with normal saline solution and contact an ophthalmologist.

- Strong inhibitors or inducers of CYP3A4 can affect the vinorelbine concentration and caution should therefore be exercised (see section 4.5).

- This product is generally not recommended in combination with live attenuated vaccines, phenytoin and itraconazole.

- For information on pregnancy, breast feeding and fertility, please refer to section 4.6.

- To avoid the risk of bronchospasm - especially in combination therapy with mitomycin C appropriate prophylaxis may be considered. Outpatients should be informed that in case of dyspnoea a doctor has to be informed.

- Because of the low level of renal excretion, there are no pharmacokinetic grounds for reducing the dose in patients with renal impairment.

4.5 Interaction with other medicinal products and other forms of interaction

The combination of vinorelbine and other drugs with known bone marrow toxicity is likely to increase the myelosuppressive adverse reactions.

CYP3A4 is the main enzyme involved in the metabolism of vinorelbine, and the combination with a drug that induces (such as phenytoin, phenobarbital, rifampicin, carbamazepine, Hypericum perforatum) or inhibits (such as itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin, nefazodone), this iso-enzyme can affect the concentration of vinorelbine (see section 4.4). Vinorelbine is a substrate for P-glycoprotein and concurrent treatment with other drugs that inhibit (i.e. ritonavir, clarithromycin, cyclosporine, verapamil, quinidine) or induce (see list of CYP 3A4 inducers given above) the same transport protein can affect the concentration of vinorelbine.

The combination vinorelbine-cisplatin (a very common combination) shows no interaction with respect to the pharmacological parameters of vinorelbine. However, a higher incidence of granulocytopenia has been reported in patients receiving combination therapy with vinorelbine and cisplatin than in those receiving vinorelbine alone.

Concomitant administration of Vinca alkaloids and mitomycin C may increase the risk of pulmonary toxicity including bronchospasm (see also section 4.4, 4.8).

Due to the increase of thrombotic risk in case of tumoural diseases, the use of anticoagulative treatment is frequent. The high intra-individual variability of the coagulability during diseases, and the eventuality of interaction between oral anticoagulants and anticancer chemotherapy require, if it is decided to treat the patient with oral anticoagulants, to increase frequency of the INR (International Normalised Ratio) monitoring.

Yellow fever vaccine is contraindicated due to the potential risk of fatal systemic vaccinal disease.

Concomitant use of live attenuated vaccines (except yellow fever) are not recommended due to the risk of systemic, possible fatal disease. This risk is increased in subjects who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where one exists (poliomyelitis).

Phenytoin: Concomitant use is not recommended. Risk of exacerbation of convulsions resulting from the decrease of phenytoin gastrointestinal absorption or risk of toxicity enhancement or reduced efficacy of the vinorelbine due to increased hepatic metabolism by phenytoin.
Itraconazole: Concomitant use is not recommended due to potential increased neurotoxicity.
Ciclosporine, Tacrolimus: Excessive immunosuppression with risk of lymphoproliferation is to be taken into consideration.

4.6 Pregnancy and lactation

Pregnancy

There are insufficient data from the use of vinorelbine in pregnant women. In animal reproductive studies vinorelbine was embryo- and foeto-lethal and teratogenic. During pregnancy this product should not be used. Fertile women should use effective methods of contraception during treatment with Vinorelbine 10 mg/ml concentrate for solution for infusion and should inform their doctor if they become pregnant. If pregnancy occurs during treatment the patient should be informed about the risks for the unborn child and be monitored carefully. The possibility of genetic counselling should be also considered.

Breast-feeding

It is not known whether vinorelbine passes into the breast milk. Breast-feeding must be discontinued before treatment with Vinorelbine 10 mg/ml concentrate for solution for infusion is commenced.

Fertility

Vinorelbine can have genotoxic effects. Therefore, men being treated with vinorelbine are advised not to father a child during and for up to 6 months (minimum 3 months) following cessation of treatment. Women of childbearing potential must use an effective method of contraception during treatment. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with vinorelbine.

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed. However, caution is necessary in patients treated with Vinorelbine considering some side effects of the drug (see section 4.8).

4.8 Undesirable effects

Bone marrow toxicity and gastrointestinal symptoms are the most frequent and relevant undesirable effects of vinorelbine in monotherapy and combined therapy.

In combined chemotherapy of vinorelbine with other antineoplastic medicinal products it has to be considered, that the listed undesirable effect can occur more frequently and more severe than those undesirable effects observed during and after monotherapy. Moreover, the additional specific undesirable effects of the other medicinal products have to be considered.

Frequencies

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Infections and infestations</th>
<th>Blood and lymphatic system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common (≥ 1/10)</td>
<td>Common Infection</td>
<td>Very common</td>
</tr>
<tr>
<td>Common (≥1/100, &lt;1/10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncommon (≥1/1,000, &lt;1/100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rare (≥1/10,000, &lt;1/1,000)</td>
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<td></td>
</tr>
<tr>
<td>Very rare (&lt;1/10,000), including isolated reports</td>
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<td></td>
</tr>
<tr>
<td>Disorders</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Neutropenia, anaemia</td>
<td>Common Thrombocytopenia, febrile neutropenia, neutropenic sepsis with potential fatal outcome</td>
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</tr>
<tr>
<td>Immune system disorders</td>
<td>Common Allergic reactions (skin reactions, respiratory reactions)</td>
<td></td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>Rare Severe hyponatraemia, Very rare SIADH-syndrome</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very common Constipation (see also „Gastrointestinal disorders“), Loss of deep tendon reflexes</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Rare Ischaemic heart disease like angina pectoris, transitory electrocardiogram modifications, myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Common Dyspnoea, bronchospasm, Rare Interstitial lung disease</td>
<td></td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Very common Constipation (see also “Nervous system disorders”), nausea, vomiting, diarrhoea, stomatitis, oesophagitis, anorexia</td>
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<tr>
<td>Hepatobiliary disorders</td>
<td>Very common Abnormal liver function values (total bilirubin increased, alkaline phosphatase increased, aspartate aminotransferase increased, alanine aminotransferase increased)</td>
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</tr>
<tr>
<td>Disorder Category</td>
<td>Frequency</td>
<td>Symptoms</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>-------------</td>
<td>--------------------------------------------------------------------------</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Very common</td>
<td>Alopecia, Common, Skin reactions, Rare, Generalised skin reactions</td>
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<td></td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Common</td>
<td>Myalgia, arthralgia, Rare, Jaw pain</td>
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<td></td>
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<tr>
<td>Renal and urinary disorders</td>
<td>Common</td>
<td>Creatinine increased</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Very common</td>
<td>Fatigue, fever, pain in different locations, asthenia, injection site erythema, injection site pain, injection site discoloration, injection site phlebitis</td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Uncommon</td>
<td>Septicaemia (very rarely fatal).</td>
</tr>
</tbody>
</table>

**Grades (G) of toxicity according to WHO classification**

**Infections and infestations**

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

**Blood and lymphatic system disorders**

The limiting toxicity is bone marrow depression which is manifested, in particular, as neutropenia (G1: 9.7%; G2: 15.2%; G3: 24.3%, G4: 27.8%), which is reversible within 5-7 days and non-cumulative; the neutrophil count is usually at its lowest 7-14 days after administration.

Febrile neutropenia and neutropenic sepsis which in some cases (1.2%) had a fatal outcome can occur.

Anaemia (G1-2: 61.2%; G3-4: 7.4% in monotherapy) and thrombocytopenia (G1-2: 5.1%; G3-4: 2.5% in monotherapy) can occur but are rarely severe.

**Immune system disorders**

Allergic reactions (skin reactions, respiratory reactions) are common.

**Metabolism and nutrition disorders**

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

**Nervous system disorders**

Peripheral nervous system
Neurological conditions will normally be restricted to loss of deep tendon reflexes.
Development of severe paraesthesias, neurosensory and neuromotor disorders can occur (G1: 17.2%, G2: 3.6%, G3: 2.6%, G4: 0.1%). Very rarely Guillain-Barré syndrome.
Weakness of the lower extremities has been reported after long-term treatment. These symptoms are generally reversible.

Autonomic nervous system
The main symptom is constipation due to intestinal paresis (G1: 16.9%; G2: 4.9%; G3: 2%; G4: 0.7%), but it rarely progresses to paralytic ileus (see also “Gastrointestinal disorders”). The incidence of such reactions can increase when vinorelbine is combined with other chemotherapy.

Cardiac disorders
Ischaemic heart disease (angina pectoris and/or transitory electrocardiogram modifications, myocardial infarction) has been reported in rare cases.

Respiratory system, thoracic and mediastinal disorders
As with other vinca alkaloids, vinorelbine can cause dyspnoea and bronchospasm. Rare cases of interstitial lung disease have been reported, especially in patients treated with vinorelbine in combination with mitomycin.

Gastrointestinal disorders
Very commonly nausea and vomiting is observed (G1: 19.9%; G2: 8.3%). Severe nausea and vomiting can occur commonly (G3: 1.9%; G4: 0.3%). The incidence of nausea and vomiting can increase when vinorelbine is combined with other chemotherapy. Antiemetic treatment can reduce the frequency.

Constipation and paralytic ileus (see also “Autonomous nervous system”). The treatment can be resumed after recovery of normal intestinal function.

Stomatitis as well as diarrhoea (G1: 7.6%; G2: 3.6%; G3: 0.7%; G4: 0.1%) and oesophagitis can occur. Severe diarrhoea is uncommon.

Anorexia is observed very commonly (G1-2: 14%; G3: 1%).

Rare cases of pancreatitis have been reported.

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

Skin and subcutaneous tissue disorders
Mild alopecia may commonly occur which progresses if the treatment is continued (G1-2: 21%; G3-4: 4.1% in monotherapy). Commonly vinorelbine can cause skin reactions and in rare cases generalised skin reactions.

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

Renal and urinary disorders
Increased blood creatinine was observed commonly.

General disorders and administration site conditions
Patients being treated with vinorelbine can have fatigue, asthenia, fever and pain in different locations such as chest pain and pain in the tumor.

Reactions at the injection site can include erythema, smarting pains, discoloration of the vein and local phlebitis (G1: 12.3%; G2: 8.2%, G3: 3.6%; G4: 0.1% in monotherapy). As other
vinca alkaloids vinorelbine has vesicant power. In rare cases local necrosis due to extravasation has been observed. This undesirable effect can be limited by correct positioning of the intravenous cannula or catheter and bolus injection, followed by liberal flushing of the vein.

4.9 Overdose
Cases of accidental acute overdose have been reported in humans:
Such cases can result in bone marrow hypoplasia and are sometimes associated with infection, fever and paralytic ileus. Supporting treatment such as blood transfusion or broad-spectrum antibiotic treatment is normally initiated at the doctor’s discretion. There is no known antidote.

As there is no specific antidote for the overdosage of vinorelbine given intravenously, symptomatic measures are necessary in case of an overdosage, e.g.:
- Continuous control of vital signs and careful monitoring of the patient.
- Daily control of blood count to observe the need of blood transfusions, of growth factors and to detect the need of intensive care and to minimize the risk of infections.
- Measures for prevention or for therapy of paralytic ileus
- Control of circulation system and of liver function
- Broad spectrum antibiotic therapy may be necessary in case of complications due to infections.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Vinca alkaloids and analogues
ATC code: L01CA04
Vinorelbine is an antineoplastic active substance of the vinca alkaloid family, but in contrast to all other vinca alkaloids the catharanthine portion of vinorelbine has undergone a structural modification. On the molecular level it affects the dynamic equilibrium of tubulin in the microtubular system of the cell.

Vinorelbine inhibits tubulin polymerisation and binds preferentially to mitotic microtubules, only affecting axonal microtubules at high concentrations. Spiralisation of the tubulin is induced to a lesser degree than with vincristine. Vinorelbine blocks mitosis in phase G2-M, causing cell death in interphase or at the following mitosis.

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

5.2 Pharmacokinetic properties
After intravenous bolus injection or infusion in patients, the plasma concentration of vinorelbine is characterised by a three exponential elimination curve. The terminal elimination phase reflects a long half-life greater than 40 hours. Total clearance of vinorelbine is high (0.97-1.26 l/h/kg).

The active ingredient is widely distributed in the body with a volume of distribution ranging from 25.4-40.1 l/kg. Penetration of vinorelbine into pulmonary tissue is significant with
tissue/plasma concentration ratios of greater than 300 in a study involving surgical biopsy. There is moderate binding to plasma proteins (13.5 %) but strong binding to platelets (78%). Linear pharmacokinetics have been shown for intravenously administered vinorelbine up to a dose of 45 mg/m².

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

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

The effect of kidney dysfunction on the disposition of vinorelbine has not been studied, but dose reduction is not indicated because of the low degree of renal excretion. In patients with liver metastases changes only occurred in the mean clearance of vinorelbine when over 75% of the liver was affected. In 6 cancer patients with moderate liver dysfunction (bilirubin ≤ 2 x ULN and aminotransferases ≤ 5 x ULN) treated with up to 25 mg/m² and 8 cancer patients with severe liver dysfunction (bilirubin> 2 x ULN and/or aminotransferases> 5 x ULN) treated with up to 20 mg/m², mean total clearance in the two groups were similar to that in patients with normal liver function. These data may however not be representative for patients with reduced drug elimination capacity of the liver and therefore caution is recommended in patients with severe hepatic impairment and careful monitoring of haematological parameters required (see section 4.2 and 4.4).

A strong relationship between the exposure of blood and reduction in leucocytes or polynuclear leucocytes has been demonstrated.

5.3 Preclinical safety data

Mutagenic and carcinogenic potential

In animal studies vinorelbine induced aneuploidy and polyploidy. It can be assumed that vinorelbine can also cause genotoxic effects in humans (aneuploidy and polyploidy). The results for carcinogenic potential in the mouse and rat were negative but only low doses have been tested.

Reproductive toxicity studies

In animal reproductive studies, effects were observed at subtherapeutic dosages. Embryo- and foetotoxicity were seen, such as intra-uterine growth retardation and delayed ossification. Teratogenicity (fusion of the vertebrae, missing ribs) was observed at maternal toxic doses. In addition, spermatogenesis and secretion of prostate and seminal vesicles were reduced, but fertility in rats was not diminished.

Safety pharmacology

Safety pharmacology studies performed in the dog and in the monkey did not reveal any adverse effect on the cardio-vascular system.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide, water for injections.

6.2 Incompatibilities

Vinorelbine 10 mg/ml concentrate for solution for infusion may not be diluted with alkaline solutions (risk of precipitation).
This medicinal product may not be mixed with any other medicines, apart from those listed in section 6.6.

6.3 **Shelf life**

*Original pack*

2 years

For single use only. Unused concentrate must be discarded after use.

*Following dilution*

Following dilution with physiological sodium chloride solution or 50 mg/ml (5%) glucose solution, the chemical and physical stability of the reconstituted solution has been confirmed for 24 hours at 2–8°C and 25°C.

On microbiological grounds, the reconstituted solution should be used immediately. If it is not used immediately, the storage time and conditions are the responsibility of the user and should normally not exceed 24 hours at 2–8°C, unless opening and dilution were performed under controlled and validated aseptic conditions.

6.4 **Special precautions for storage**

Store in the refrigerator (2–8°C).

Store in the original package, in order to protect from light.

6.5 **Nature and contents of container**

Type 1 glass vial with butyl rubber stopper laminated with fluororesin and aluminium closure.

Pack sizes: 1 ml or 5 ml concentrate in packs of 1 or 10 vials are available.

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**

The preparation and administration of vinorelbine should be carried out only by trained personnel. Suitable protective goggles, disposable gloves and disposable clothing must be worn. Spills and leakages must be wiped up.

Any contact with the eyes must be strictly avoided. If the solution does come into contact with the eyes they must be rinsed immediately with plenty of physiological saline.

After preparation, any exposed surface must be thoroughly cleaned and hands and face washed.

There is no incompatibility between the contents and container for Vinorelbine 10 mg/ml Concentrate for solution for infusion and a neutral glass bottle, PVC bag, vinylacetate bag or infusion set with PVC tubes.

It is recommended to administer vinorelbine as an infusion over the course of 5-10 minutes after dilution in 20-50 ml physiological saline or glucose 50 mg/ml (5%) solution or by a short infusion (20-30 minutes) after dilution in 125 ml of normal saline or glucose 50 mg/ml (5%) solution. After administration the vein must be flushed through thoroughly with at least 250 ml isotonic solution.

Unused medicinal product and waste must be disposed of in accordance with local requirements.
MARKETING AUTHORISATION HOLDER
Pharmaceutical Works POLPHARMA SA
19 Pelplińska Street, 83-200 Starogard Gdański, Poland

MARKETING AUTHORISATION NUMBER(S)
PL 25124/0014

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
11/05/2009

DATE OF REVISION OF THE TEXT
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Vinorelbine 50 mg/5 ml, concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5 ml vial contains a total content of vinorelbine (as tartrate) of 50 mg
Each ml contains 10 mg of vinorelbine (as tartrate).
For excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Concentrate for solution for infusion
Clear, colourless solution with a pH of 3.3 to 3.8 and an osmolarity 47 mOsm/kg.

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 infusion only.
Vinorelbine 10 mg/ml concentrate for solution for infusion should be given in cooperation with a physician with extensive experience in therapy with cytostatics.
The use of intrathecal route is contra-indicated.
For instructions on dilution of the product before administration, see section 6.6.
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 normal saline or glucose 50 mg/ml (5%) solution or by a short infusion (20-30 minutes) after dilution in 125 ml of normal saline or glucose 50 mg/ml (5%) solution. Administration should always be followed with at least 250 ml of an isotonic solution to flush the vein.

Non-small cell lung cancer
As a single agent the normal dose is 25-30 mg/m², administered once weekly. In polychemotherapy the schedule regimen is a function of the protocol. The normal dose could be used (25-30 mg/m²), but the frequency of the administration be reduced to for example day 1 and 5 every third week or day 1 and 8 every third week according to the regimen.

Advanced or metastatic breast cancer
The normal dose is 25-30 mg/m², administered once weekly.
The maximum tolerated dose per administration: 35.4 mg/m² body surface area.
Vinorelbine is not recommended for use in children due to a lack of data on safety and efficacy: see section 5.1.
For patients with severely reduced hepatic function caution and careful monitoring of haematological parameters is recommended. The dose may have to be reduced (see sections 4.4 and 5.2).

In patients with reduced kidney function, the dose does not have to be adjusted (see section 5.2).

Elderly: No dose reduction is required.

4.3 Contraindications
The use of intrathecal route is contraindicated.
Hypersensitivity to vinorelbine or other Vinca alkaloids.
Neutrophil granulocytes < 1.5 x 10^9/l or serious, current or recent infection (within 2 weeks).
Platelet count below 7.5 x 10^10/l.
Pregnancy.
Breast-feeding should be discontinued during treatment with vinorelbine (see section 4.6).
Severe hepatic impairment not related to the tumoral process.
Women of childbearing potential not using effective contraception (see sections 4.4 and 4.6).
In combination with yellow fever vaccine (see section 4.5).

4.4 Special warnings and precautions for use
Strictly for intravenous use only.
Vinorelbine should be administered under the supervision of a physician experienced in the use of chemotherapy.

Close haematological monitoring should be performed during treatment (determination of haemoglobin level and number of leucocytes, neutrophils and platelets before each new infusion), since inhibition of the haematopoietic system is the main risk during treatment with vinorelbine.

- Neutropenia, which is non-cumulative and has its nadir between day 7 and 14 after administration, and is quickly reversible within 5-7 days, is the main dose-limiting adverse reaction. If the number of neutrophil granulocytes is below 1.5 x 10^9/l and/or the platelet count is below 7.5 x 10^10/l, the treatment should be postponed until recovery.
- If the patient presents signs or symptoms suggestive of infection, a prompt investigation should be carried out.
- Special caution is advised in patients with a history of ischaemic heart disease.
- The clinical relevance of impaired drug elimination capacity of the liver has not been characterised. Therefore no exact dose recommendation could be given. However in the pharmacokinetic study the highest administered dose in patients with severe liver dysfunction was 20 mg/m² (see section 5.2). For patients with severe hepatic impairment caution is recommended and careful monitoring of haematological parameters is required. Dosage reduction may also be required (see sections 4.2 and 4.3).

- Vinorelbine 10 mg/ml concentrate for solution for infusion should not be given concomitantly with radiotherapy if the treatment field includes the liver.
- Vinorelbine 10 mg/ml concentrate for solution for infusion must not get into contact with the eye; risk of severe irritation and even corneal ulceration if the drug is sprayed under pressure. If this occurs, immediately rinse the eye with normal saline solution and contact an ophthalmologist.
- Strong inhibitors or inducers of CYP3A4 can affect the vinorelbine concentration and caution should therefore be exercised (see section 4.5).
- This product is generally not recommended in combination with live attenuated vaccines, phenytoin and itraconazole.
- For information on pregnancy, breast feeding and fertility, please refer to section 4.6.
- To avoid the risk of bronchospasm - especially in combination therapy with mitomycin C appropriate prophylaxis may be considered. Outpatients should be informed that in case of dyspnoea a doctor has to be informed.
- Because of the low level of renal excretion, there are no pharmacokinetic grounds for reducing the dose in patients with renal impairment.

4.5 Interaction with other medicinal products and other forms of interaction

The combination of vinorelbine and other drugs with known bone marrow toxicity is likely to increase the myelosuppressive adverse reactions.

CYP3A4 is the main enzyme involved in the metabolism of vinorelbine, and the combination with a drug that induces (such as phenytoin, phenobarbital, rifampicin, carbamazepine, Hypericum perforatum) or inhibits (such as itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin, nefazodone), this iso-enzyme can affect the concentration of vinorelbine (see section 4.4). Vinorelbine is a substrate for P-glycoprotein and concurrent treatment with other drugs that inhibit (i.e. ritonavir, clarithromycin, cyclosporine, verapamil, quinidine) or induce (see list of CYP 3A4 inducers given above) the same transport protein can affect the concentration of vinorelbine.

The combination vinorelbine-cisplatin (a very common combination) shows no interaction with respect to the pharmacological parameters of vinorelbine. However, a higher incidence of granulocytopenia has been reported in patients receiving combination therapy with vinorelbine and cisplatin than in those receiving vinorelbine alone.

Concomitant administration of Vinca alkaloids and mitomycin C may increase the risk of pulmonary toxicity including bronchospasm (see also section 4.4, 4.8).

Due to the increase of thrombotic risk in case of tumoural diseases, the use of anticoagulative treatment is frequent. The high intra-individual variability of the coagulability during diseases, and the eventuality of interaction between oral anticoagulants and anticancer chemotherapy require, if it is decided to treat the patient with oral anticoagulants, to increase frequency of the INR (International Normalised Ratio) monitoring.

Yellow fever vaccine is contraindicated due to the potential risk of fatal systemic vaccinal disease.

Concomitant use of live attenuated vaccines (except yellow fever) are not recommended due to the risk of systemic, possible fatal disease. This risk is increased in subjects who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where one exists (poliomyelitis).

Phenytoin: Concomitant use is not recommended. Risk of exacerbation of convulsions resulting from the decrease of phenytoin gastrointestinal absorption or risk of toxicity enhancement or reduced efficacy of the vinorelbine due to increased hepatic metabolism by phenytoin.

Itraconazole: Concomitant use is not recommended due to potential increased neurotoxicity.

Ciclosporine, Tacrolimus: Excessive immunosuppression with risk of lymphoproliferation is to be taken into consideration.

4.6 Pregnancy and lactation

Pregnancy
There are insufficient data from the use of vinorelbine in pregnant women. In animal reproductive studies vinorelbine was embryo- and foeto-lethal and teratogenic. During pregnancy this product should not be used. Fertile women should use effective methods of contraception during treatment with Vinorelbine 10 mg/ml concentrate for solution for infusion and should inform their doctor if they become pregnant. If pregnancy occurs during treatment the patient should be informed about the risks for the unborn child and be monitored carefully. The possibility of genetic counselling should be also considered.

**Breast-feeding**

It is not known whether vinorelbine passes into the breast milk. Breast-feeding must be discontinued before treatment with Vinorelbine 10 mg/ml concentrate for solution for infusion is commenced.

**Fertility**

Vinorelbine can have genotoxic effects. Therefore, men being treated with vinorelbine are advised not to father a child during and for up to 6 months (minimum 3 months) following cessation of treatment. Women of childbearing potential must use an effective method of contraception during treatment. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with vinorelbine.

### 4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed. However, caution is necessary in patients treated with Vinorelbine considering some side effects of the drug (see section 4.8).

### 4.8 Undesirable effects

Bone marrow toxicity and gastrointestinal symptoms are the most frequent and relevant undesirable effects of vinorelbine in monotherapy and combined therapy.

In combined chemotherapy of vinorelbine with other antineoplastic medicinal products it has to be considered, that the listed undesirable effect can occur more frequently and more severe than those undesirable effects observed during and after monotherapy. Moreover, the additional specific undesirable effects of the other medicinal products have to be considered.

**Frequencies**

<table>
<thead>
<tr>
<th>Very common (≥1/10)</th>
<th>Common (≥1/100, &lt;1/10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon (≥1/1,000, &lt;1/100)</td>
<td>Rare (≥1/10,000, &lt;1/1,000)</td>
</tr>
<tr>
<td>Very rare (&lt;1/10,000), including isolated reports</td>
<td></td>
</tr>
</tbody>
</table>

**Infections and infestations**

<table>
<thead>
<tr>
<th>Common Infection</th>
</tr>
</thead>
</table>

**Blood and lymphatic system disorders**

| Very common Neutropenia, anaemia |
| Common Thrombocytopenia, febrile neutropenia, neutropenic sepsis with potential fatal outcome |

**Immune system disorders**

<table>
<thead>
<tr>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category</td>
</tr>
<tr>
<td>----------------------------------------------</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Common</td>
</tr>
</tbody>
</table>
### Rare
- Generalised skin reactions

### Common
- Myalgia, arthralgia

### Rare
- Jaw pain

### Generalised skin reactions

### Musculoskeletal and connective tissue disorders

### Renal and urinary disorders

### General disorders and administration site conditions

### Infections and infestations

<table>
<thead>
<tr>
<th>Grades (G) of toxicity according to WHO classification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and infestations</strong></td>
</tr>
<tr>
<td>Infections can develop commonly, mainly due to bone marrow suppression.</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
</tr>
<tr>
<td>The limiting toxicity is bone marrow depression which is manifested, in particular, as neutropenia (G1: 9.7%; G2: 15.2%; G3: 24.3%, G4: 27.8%), which is reversible within 5-7 days and non-cumulative; the neutrophil count is usually at its lowest 7-14 days after administration.</td>
</tr>
<tr>
<td>Febrile neutropenia and neutropenic sepsis which in some cases (1.2%) had a fatal outcome can occur.</td>
</tr>
<tr>
<td>Anaemia (G1-2: 61.2%; G3-4: 7.4% in monotherapy) and thrombocytopenia (G1-2: 5.1%; G3-4: 2.5% in monotherapy) can occur but are rarely severe.</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
</tr>
<tr>
<td>Allergic reactions (skin reactions, respiratory reactions) are common.</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
</tr>
<tr>
<td>Rare cases of severe hyponatraemia and in very rare cases SIADH-syndrome (syndrome of inappropriate antidiuretic hormone secretion) have been reported.</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
</tr>
<tr>
<td>Peripheral nervous system</td>
</tr>
<tr>
<td>Neurological conditions will normally be restricted to loss of deep tendon reflexes.</td>
</tr>
<tr>
<td>Development of severe paraesthesias, neurosensory and neuromotor disorders can occur (G1: 17.2%, G2: 3.6%, G3: 2.6%, G4: 0.1%). Very rarely Guillain-Barré syndrome.</td>
</tr>
<tr>
<td>Weakness of the lower extremities has been reported after long-term treatment. These symptoms are generally reversible.</td>
</tr>
<tr>
<td><strong>Autonomic nervous system</strong></td>
</tr>
</tbody>
</table>
The main symptom is constipation due to intestinal paresis (G1: 16.9%; G2: 4.9%; G3: 2%; G4: 0.7%), but it rarely progresses to paralytic ileus (see also “Gastrointestinal disorders”). The incidence of such reactions can increase when vinorelbine is combined with other chemotherapy.

**Cardiac disorders**

Ischaemic heart disease (angina pectoris and/or transitory electrocardiogram modifications, myocardial infarction) has been reported in rare cases.

**Respiratory system, thoracic and mediastinal disorders**

As with other vinca alkaloids, vinorelbine can cause dyspnoea and bronchospasm. Rare cases of interstitial lung disease have been reported, especially in patients treated with vinorelbine in combination with mitomycin.

**Gastrointestinal disorders**

Very commonly nausea and vomiting is observed (G1: 19.9%; G2: 8.3%). Severe nausea and vomiting can occur commonly (G3: 1.9%; G4: 0.3%). The incidence of nausea and vomiting can increase when vinorelbine is combined with other chemotherapy. Antiemetic treatment can reduce the frequency.

Constipation and paralytic ileus (see also “Autonomic nervous system”). The treatment can be resumed after recovery of normal intestinal function.

Stomatitis as well as diarrhoea (G1: 7.6%; G2: 3.6%; G3: 0.7%; G4: 0.1%) and oesophagitis can occur. Severe diarrhoea is uncommon.

Anorexia is observed very commonly (G1-2: 14%; G3: 1%).

Rare cases of pancreatitis have been reported.

**Hepatobiliary disorders**

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

**Skin and subcutaneous tissue disorders**

Mild alopecia may commonly occur which progresses if the treatment is continued (G1-2: 21%; G3-4: 4.1% in monotherapy). Commonly vinorelbine can cause skin reactions and in rare cases generalised skin reactions.

**Musculoskeletal and connective tissue disorders**

Arthralgia including jaw pain and myalgia have been reported in patients being treated with vinorelbine.

**Renal and urinary disorders**

Increased blood creatinine was observed commonly.

**General disorders and administration site conditions**

Patients being treated with vinorelbine can have fatigue, asthenia, fever and pain in different locations such as chest pain and pain in the tumor.

Reactions at the injection site can include erythema, smarting pains, discoloration of the vein and local phlebitis (G1: 12.3%; G2: 8.2%, G3: 3.6%; G4: 0.1% in monotherapy). As other vinca alkaloids vinorelbine has vesicant power. In rare cases local necrosis due to extravasation has been observed. This undesirable effect can be limited by correct positioning of the intravenous cannula or catheter and bolus injection, followed by liberal flushing of the vein.
4.9 Overdose
Cases of accidental acute overdose have been reported in humans:

Such cases can result in bone marrow hypoplasia and are sometimes associated with infection, fever and paralytic ileus. Supporting treatment such as blood transfusion or broad-spectrum antibiotic treatment is normally initiated at the doctor's discretion. There is no known antidote.

As there is no specific antidote for the overdosage of vinorelbine given intravenously, symptomatic measures are necessary in case of an overdosage, e.g.:

- Continuous control of vital signs and careful monitoring of the patient.
- Daily control of blood count to observe the need of blood transfusions, of growth factors and to detect the need of intensive care and to minimize the risk of infections.
- Measures for prevention or for therapy of paralytic ileus
- Control of circulation system and of liver function
- Broad spectrum antibiotic therapy may be necessary in case of complications due to infections.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Vinca alkaloids and analogues
ATC code: L01CA04

Vinorelbine is an antineoplastic active substance of the vinca alkaloid family, but in contrast to all other vinca alkaloids the catharanthine portion of vinorelbine has undergone a structural modification. On the molecular level it affects the dynamic equilibrium of tubulin in the microtubular system of the cell.

Vinorelbine inhibits tubulin polymerisation and binds preferentially to mitotic microtubules, only affecting axonal microtubules at high concentrations. Spiralisation of the tubulin is induced to a lesser degree than with vincristine. Vinorelbine blocks mitosis in phase G2-M, causing cell death in interphase or at the following mitosis.

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

5.2 Pharmacokinetic properties
After intravenous bolus injection or infusion in patients, the plasma concentration of vinorelbine is characterised by a three exponential elimination curve. The terminal elimination phase reflects a long half-life greater than 40 hours. Total clearance of vinorelbine is high (0.97-1.26 l/h/kg).

The active ingredient is widely distributed in the body with a volume of distribution ranging from 25.4-40.1 l/kg. Penetration of vinorelbine into pulmonary tissue is significant with tissue/plasma concentration ratios of greater than 300 in a study involving surgical biopsy. There is moderate binding to plasma proteins (13.5 %) but strong binding to platelets (78%). Linear pharmacokinetics have been shown for intravenously administered vinorelbine up to a dose of 45 mg/m².

Vinorelbine is primarily metabolised by CYP3A4 of cytochrome P450. All metabolites have been identified and none are active with the exception of 4-O-deacetylvinorelbine, which is the principal metabolite in the blood.
Renal elimination is low (<20% of the dose). Small concentrations of deacetyl vinorelbine have been recovered in humans, but vinorelbine is principally detected as the unchanged compound in urine. Elimination of the active substance is mainly via the bile duct and consists of the metabolites and mainly of unchanged vinorelbine.

The effect of kidney dysfunction on the disposition of vinorelbine has not been studied, but dose reduction is not indicated because of the low degree of renal excretion. In patients with liver metastases changes only occurred in the mean clearance of vinorelbine when over 75% of the liver was affected. In 6 cancer patients with moderate liver dysfunction (bilirubin ≤ 2 x ULN and aminotransferases ≤ 5 x ULN) treated with up to 25 mg/m² and 8 cancer patients with severe liver dysfunction (bilirubin > 2 x ULN and/or aminotransferases > 5 x ULN) treated with up to 20 mg/m², mean total clearance in the two groups were similar to that in patients with normal liver function. These data may however not be representative for patients with reduced drug elimination capacity of the liver and therefore caution is recommended in patients with severe hepatic impairment and careful monitoring of haematological parameters required (see section 4.2 and 4.4).

A strong relationship between the exposure of blood and reduction in leucocytes or polynuclear leucocytes has been demonstrated.

5.3 Preclinical safety data

**Mutagenic and carcinogenic potential**

In animal studies vinorelbine induced aneuploidy and polyploidy. It can be assumed that vinorelbine can also cause genotoxic effects in humans (aneuploidy and polyploidy). The results for carcinogenic potential in the mouse and rat were negative but only low doses have been tested.

**Reproductive toxicity studies**

In animal reproductive studies, effects were observed at subtherapeutic dosages. Embryo- and foetotoxicity were seen, such as intra-uterine growth retardation and delayed ossification. Teratogenicity (fusion of the vertebrae, missing ribs) was observed at maternal toxic doses. In addition, spermatogenesis and secretion of prostate and seminal vesicles were reduced, but fertility in rats was not diminished.

**Safety pharmacology**

Safety pharmacology studies performed in the dog and in the monkey did not reveal any adverse effect on the cardio-vascular system.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide, water for injections.

6.2 Incompatibilities

*Vinorelbine 10 mg/ml concentrate for solution for infusion* may not be diluted with alkaline solutions (risk of precipitation).

This medicinal product may not be mixed with any other medicines, apart from those listed in section 6.6.

6.3 Shelf life

*Original pack*

2 years
For single use only. Unused concentrate must be discarded after use.

Following dilution

Following dilution with physiological sodium chloride solution or 50 mg/ml (5%) glucose solution, the chemical and physical stability of the reconstituted solution has been confirmed for 24 hours at 2–8°C and 25°C.

On microbiological grounds, the reconstituted solution should be used immediately. If it is not used immediately, the storage time and conditions are the responsibility of the user and should normally not exceed 24 hours at 2–8°C, unless opening and dilution were performed under controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in the refrigerator (2–8°C).

Store in the original package, in order to protect from light.

6.5 Nature and contents of container

Type 1 glass vial with butyl rubber stopper laminated with fluororesin and aluminium closure.

Pack sizes: 1 ml or 5 ml concentrate in packs of 1 or 10 vials are available.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The preparation and administration of vinorelbine should be carried out only by trained personnel. Suitable protective goggles, disposable gloves and disposable clothing must be worn. Spills and leakages must be wiped up.

Any contact with the eyes must be strictly avoided. If the solution does come into contact with the eyes they must be rinsed immediately with plenty of physiological saline.

After preparation, any exposed surface must be thoroughly cleaned and hands and face washed.

There is no incompatibility between the contents and container for Vinorelbine 10 mg/ml Concentrate for solution for infusion and a neutral glass bottle, PVC bag, vinylacetate bag or infusion set with PVC tubes.

It is recommended to administer vinorelbine as an infusion over the course of 5-10 minutes after dilution in 20-50 ml physiological saline or glucose 50 mg/ml (5%) solution or by a short infusion (20-30 minutes) after dilution in 125 ml of normal saline or glucose 50 mg/ml (5%) solution. After administration the vein must be flushed through thoroughly with at least 250 ml isotonic solution.

Unused medicinal product and waste must be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Pharmaceutical Works POLPHARMA SA

19 Pelplińska Street, 83-200 Starogard Gdański, Poland

8 MARKETING AUTHORISATION NUMBER(S)

PL 25124/0015
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/05/2009

10 DATE OF REVISION OF THE TEXT
Module 3

Product Information Leaflet
PACKAGE LEAFLET: INFORMATION FOR THE USER

Vinorelbine Polpharma, 10 mg/ml, concentrate for solution for infusion
Vinorelbine Polpharma 50 mg/5 ml, concentrate for solution for infusion

Vinorelbine

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

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

1. WHAT VINORELBINE POLPHARMA IS AND WHAT IT IS USED FOR

Vinorelbine belongs to a group of medicines known as vinca alkaloids, which are used in the treatment of cancer.

Vinorelbine Polpharma has been prescribed by your doctor for the treatment of advanced breast cancer or special forms of lung cancer (non-small cell lung cancer).

2. BEFORE YOU TAKE VINORELBINE POLPHARMA

You will not be given vinorelbine:

- if you are allergic (hypersensitive) to vinorelbine or other Vinca alkaloids
- if you have or recently had serious infection or severe decrease in white blood cells (neutropenia)
- if you have severe decrease in blood platelets
- if you are pregnant
- if you are breast-feeding
- if you are women of childbearing potential not using effective contraception
- if you have a severe liver disease not caused by cancer
- in combination with yellow fever vaccine.

This medicine is strictly for intravenous use only and should not be injected into the spine.

Take special care with vinorelbine:

- if you have had a heart disease involving lack of blood supply to the heart (ischaemic heart disease, angina)
• if you are having radiotherapy and the treatment field includes the liver
• if you present signs or symptoms suggestive of infection (such as fever, chills, sore throat), let your doctor know immediately, so that he/she can carry out any tests which may be needed
• if you have impaired liver function
• if you need a vaccination. You should inform your doctor of the treatment before any vaccinations.
• if you receive a cancer medicine named mitomycin C.

Vinorelbine must not get into contact with the eye as there is a risk of severe irritation and even corneal ulceration. If this occurs, immediately rinse the eye with normal saline solution and contact an ophthalmologist.

Men and women who are treated with vinorelbine should use an effective contraception during treatment. Men and women should both read the information under pregnancy and breast-feeding below.

Before each administration of vinorelbine a blood sample will be taken for analysis of its components. If the results of this analysis are not satisfactory, your treatment may be delayed and further checks made until these values return to normal.

Taking other medicines

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is especially important if you are using any of the following medicines:

• other medicines which can affect the bone marrow e.g. cancer medicines
• carbamazepine, phenytoin and phenobarbital (medicines for the treatment of epilepsy)
• antibiotics such as rifampicin, erythromycin, clarithromycin, telithromycin
• St John’s Worth (Hypericum perforatum)
• ketoconazole and itraconazole (medicines for the treatment of fungal infections)
• antiviral medicines to treat HIV-infection e.g. ritonavir (HIV protease inhibitors)
• nefazodon (medicine for the treatment of depression)
• cyclosporine and tacrolimus (medicine which decrease the activity of the immune system)
• verapamil, quinidine (medicines for the treatment of heart diseases)
• other medicines for the treatment of cancer e.g. mitomycin C, cisplatin
• blood thinning medicines e.g. warfarin
• yellow fever vaccine and other live vaccines.

Pregnancy and breast-feeding

Vinorelbine should not be given to pregnant women, because it can cause serious birth defects. If you are a women of childbearing age you must use an effective method of contraception during treatment. If pregnancy occurs during your treatment you must immediately inform your doctor. If you are or become pregnant during treatment with vinorelbine, genetic counselling is recommended.

If you are a man, you should avoid fathering a child during treatment with vinorelbine and for 6 months after treatment has stopped. There is also a risk that treatment with vinorelbine will lead to male infertility and you may wish to seek advice about sperm storage before the treatment starts.

You must discontinue breast-feeding before treatment with vinorelbine starts as it is not known whether it might pass into breast milk thereby affecting the baby.

Ask your doctor or pharmacist for advice before taking any medicine.
Driving and using machines
No studies of the effects on the ability to drive and use machines have been performed.

3. HOW TO TAKE VINORELBINE POLPHARMA

Vinorelbine Polpharma will be given to you under the supervision of a doctor specialized in this type of treatment.

The dosage of vinorelbine depends on the condition you are being treated for, your response to the therapy and other medication you are being given. Your general condition and your response to the treatment will be closely observed before, during and after the vinorelbine treatment.

The usual dosage of vinorelbine is 25-30 mg/m² of body surface area given once a week.

The medicine should be diluted before use with a solution of sodium chloride or glucose and given into a vein as an injection over 5-10 minutes or by infusion (drip) over 20-30 minutes. Following your treatment a solution of sodium chloride will be used to flush the vein.

Dosage will be reduced if you have severe liver problems.

The safety and efficacy in children have not been determined.

If you use Vinorelbine Polpharma more than you should
As this medicine will be given to you whilst you are in hospital it is unlikely that you will be given too little or too much. However, tell your doctor or pharmacist if you have any concerns.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Vinorelbine Polpharma can cause side effects, although not everybody gets them. Your doctor will discuss these with you and will explain the potential risks and benefits of your treatment.

You should contact your doctor immediately if you develop any allergic (hypersensitive) reactions to vinorelbine, including skin rashes, breathing difficulties. They are serious and need immediate medical attention.

The hospital staff will monitor your condition closely during treatment. Tell them immediately if you notice any of these effects.

Between infusions of Vinorelbine Polpharma the following may occur, and the frequency may vary with the combinations of drugs that are received:

Very common (experienced in more than 1 in 10 patients)
- decrease in the number of red (anaemia), or white blood cells (which are important in fighting infection)
- fever: if this happens you must tell your doctor immediately
- stomach upsets including nausea, vomiting and diarrhoea, constipation
- inflammation of oral mucosa (the lining of the inside of the mouth) or oesophagus (throat)
- loss of appetite (anorexia), raised liver enzymes (hence the need for regular blood tests)
- hair loss, tiredness
- at the injection site: pain, phlebitis (inflammation of the vein), skin colour disorder, redness of the skin.
Common (experienced in less than 1 in 10 but more than 1 in 100 patients)
- infections
- decrease in the number of platelets (may cause unusual bleeding or bruising)
- feeling of numbness or pins and needles
- suppression of some reflex reactions, occasionally altered touch awareness
- shortness of breath, joint and muscle pain
- increased blood creatinine
- skin reactions.

Uncommon (experienced in less than 1 in 100 but more than 1 in 1000 patients)
- blood poisoning (very rarely fatal).

Rare (experienced in less than 1 in 1000 but more than 1 in 10,000)
- low blood sodium
- weakness of legs
- inflammation of pancreas
- paralysis of the gut
- angina pectoris (chest pain), heart attack, changes in electrocardiogram
- jaw pain
- any extravasation may induce local reactions which rarely progress to necrosis (death of cells and/or tissues).

Very rare (experienced in less than 1 in 10,000 patients)
- SIADH-syndrome, which may include symptoms of increased weight, nausea (feeling sick), vomiting, muscle cramps, confusion and seizures (fits)
- Guillain-Barré syndrome (inflammation in peripheral nerves which may cause weakness).

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

5. HOW TO STORE VINORELBINE POLPHARMA

Keep out of the reach and sight of children.

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

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

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Vinorelbine Polpharma contains

- The active substance is vinorelbine (as tartrate).
Each 1 ml vial contains a total content of vinorelbine of 10 mg.
Each 5 ml vial contains a total content of vinorelbine of 50 mg.

- The other ingredients are sodium hydroxide, water for injections.
What Vinorelbine Polpharma looks like and contents of the pack

Vinorelbine Polpharma concentrate for solution for infusion is clear, colourless solution with a pH of 3.3 to 3.8 and an osmolarity 47 mOsm/kg.

Contents of the pack
1 ml or 5 ml concentrate in glass vials with butyl rubber stopper laminated with fluororesin and aluminium closure.
Pack size: 1 or 10 vials. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Pharmaceutical Works POLPHARMA SA
19 Pelplinska Street, 83-200 Starogard Gdański, Poland

This leaflet was last approved in

THE FOLLOWING INFORMATION IS INTENDED FOR MEDICAL OR HEALTHCARE PROFESSIONALS ONLY:

Please refer to the summary of product characteristics for detailed information regarding this product.

Handling and disposal
The preparation of injectable solutions of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicines used, in conditions that guarantee the protection of the environment and, in particular, the protection of the personnel handling the medicines. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or drink in this area. Personnel must be provided with appropriate handling materials, notably sleeved gowns, protection masks, caps, protective goggles, sterile single-use gloves, protective covers for the work area and collection bags for waste.
Syringes and infusion sets should be assembled carefully to avoid leakage (use of Luer lock fittings is recommended).

Spills and leakages must be wiped up.

Precautions should be taken to avoid exposing staff during pregnancy.
All contact with eyes must be strictly avoided.
Immediate washing of the eye with normal saline solution should be undertaken if any contact occurs.
In case of irritation contact an ophthalmologist.

In case of skin contact, thoroughly wash the affected area with water.

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

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

Incompatibilities
Vinorelbine should not be diluted in alkaline solutions (risk of precipitation).
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section “Dilution and administration”.

There is no incompatibility between vinorelbine and glass vials, PVC bag, polyethylene vial or propylene syringe.

**Dilution and administration**

Vinorelbine should only be given intravenously and after dilution.

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

It is very important to make sure that the cannula is accurately placed in the vein before the injection is commenced. If vinorelbine infiltrates the surrounding tissue during intravenous administration, a substantial irritation may occur. In this case, the injection should be stopped, the vein flushed with saline solution and the rest of the dose should be administered in another vein.

In the event of extravasation, glucocorticoids could be given intravenously to reduce the risk of phlebitis.

Excreta and vomit must be handled with care.

**Storage**

As package 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. Do not use after the expiry date which is stated on the carton.

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

After dilution: 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 and 25°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.
Module 4

Labelling
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING
(CARTON BOX)

<table>
<thead>
<tr>
<th>PART (CARTON BOX)</th>
</tr>
</thead>
</table>

### 1. NAME OF THE MEDICINAL PRODUCT

Vinorelbine Polpharma, 10 mg/ml, concentrate for solution for infusion  
Vinorelbine Polpharma, 50 mg/5 ml, concentrate for solution for infusion  
Vinorelbine

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

<table>
<thead>
<tr>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ml concentrate contains 10 mg vinorelbine (as tartrate).</td>
</tr>
<tr>
<td>Each 1 ml vial contains 10 mg vinorelbine (as tartrate).</td>
</tr>
<tr>
<td>Each 5 ml vial contains 50 mg vinorelbine (as tartrate).</td>
</tr>
</tbody>
</table>

### 3. LIST OF EXCIPIENTS

Also contains: sodium hydroxide, water for injections.

### 4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 x 1 ml vial (10 mg)</td>
<td></td>
</tr>
<tr>
<td>10 x 1 ml vial (10 mg)</td>
<td></td>
</tr>
<tr>
<td>1 x 5 ml vial (50 mg)</td>
<td></td>
</tr>
<tr>
<td>10 x 5 ml vial (50 mg)</td>
<td></td>
</tr>
</tbody>
</table>

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Cytostatic agent

MUST BE DILUTED BEFORE USE.

Intravenous use.

FATAL if given by other routes.

### 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp. Date:

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

(logo) POLPHARMA
Pharmaceutical Works POLPHARMA SA
19 Pelplinska Street, 83-200 Starogard Gdanski, Poland

12. MARKETING AUTHORISATION NUMBER(S)

Reg. N°

13. BATCH NUMBER

Batch No:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.
POM (UK only)

15. INSTRUCTIONS ON USE

Use as directed by a doctor (UK only)
16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.
Module 5

Scientific discussion during initial procedure

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Vinorelbine Polpharma 10 mg/ml concentrate for solution for infusion, in the treatment of advanced breast and non small cell lung cancer, is approvable. The market authorisations were granted on the 11/05/2009.

EXECUTIVE SUMMARY

Problem statement

This decentralised application concerns a generic version of Vinorelbine Tartrate submitted under Article 10(1), EU Directive 2001/83/EC. The originator product is Navelbine® 10 mg/ml concentrate for solution for infusion by Pierre Fabre Medicament, registered in France since 11th April 1989.

With the UK as the Reference Member State in this Decentralised Procedure, Pharmaceuticals Works Polpharma SA the CMS were BG, CZ, EE, HU, LT, LV, PL, RO, SK.

About the product

The active substance vinorelbine tartrate is a vinca alkaloid with a broad spectrum of anti-tumour activity. Vinorelbine is licensed in EU for the treatment of stage 3 and 4 non-small cell lung cancer (NSCLC) and the treatment of advanced breast cancer relapsing after or refractory to an anthracycline containing regimen.

Vinorelbine is a cytostatic antineoplastic drug. Vinorelbine and other vinca alkaloids are 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 indications applied for include:

• 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.

RMS comments:
The indication and posology are in line with the reference product.

General comments on the submitted dossier

The submitted dossier is of adequate standard.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for the product types at all...
sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

**SCIENTIFIC OVERVIEW AND DISCUSSION**

**Quality aspects**

**Drug substance**

The chemical-pharmaceutical documentation and Quality overall summary in relation to Vinorelbine 10mg/ml solution for infusion are of an acceptable quality in view of the present European regulatory requirements. The active substance Vinorelbine tartrate is described in the European Pharmacopoeia. The specification provided is adequate and batch data are in compliance with the specification. Based on the stability data a proposed re-test period of 6 months is considered acceptable.

**Drug Product**

The development of the Vinorelbine tartrate 10mg/ml solution for infusion has been adequately described. The product specifications generally cover appropriate parameters for this dosage form adequately. The analytical methods used for finished product analysis are suitably validated. Batch analysis has been performed on two batches for each presentation at pilot scale and shows the finished product meet the proposed specification. The conditions used in the stability studies are in accordance to the ICH stability guideline. Based on the stability data the proposed shelf-life of 24 months is considered acceptable.

**Non clinical aspects**

The pharmacodynamic, pharmacokinetic and toxicological properties of vinorelbine tartrate are well known. As vinorelbine tartrate is a widely used, well known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on the literature is thus appropriate. The non-clinical overview has been written by a suitably qualified person and is acceptable.

Section 5.3 of the SPC s acceptable.

**Clinical aspects**

**Pharmacokinetics**

After intravenous administration, the blood concentration-time profile, is characterised by a three exponential elimination curve. The terminal half-life was around 40 hours. Clearance in blood is high, close to the hepatic blood flow while the volume of distribution at steady-state was large showing signs of extensive tissue distribution. There is weak binding to plasma proteins but strong binding to blood cells, especially to platelets. The pharmacokinetic properties for intravenously administered vinorelbine have shown to be linear up to the dose level 45 mg/m2.

Vinorelbine is mainly metabolised by CYP3A4.
Renal excretion is low. Excretion via the biliary route is the most important route of elimination.

**RMS Assessor's comment:**
The applicant has not submitted a bioequivalence study comparing the applicant's product with the reference product. The applicant is not required to submit a bioequivalence study as the product is to be administered intravenously as an aqueous solution containing the same active substance in the same concentration as the reference product. This is in line with current guidelines (CPMP/EWP/QWP/1401/98).

**Pharmacodynamics**

Vinorelbine is a cytostatic drug of the vinca alkaloid family. Vinorelbine inhibits tubulin polymerisation and binds preferentially to mitotic microtubules. Vinorelbine blocks mitosis at G2-M, causing cell death in interphase or at the following mitosis.

**Clinical efficacy**

No new efficacy data have been submitted and none are required for this application.

**Clinical safety**

No new safety data have been submitted and none are required for this application.

**Pharmacovigilance system**

The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant 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.

**Risk Management Plan**

This is a generic application for which no special concerns have arisen and therefore no specific RMP is planned.

**BENEFIT RISK ASSESSMENT**

The benefit/risk assessment is favourable.
Module 6

Steps taken after procedure

There have been no non confidential changes to the market authorisations.