

**VINORELBINE 10MG/ML STERILE CONCENTRATE
PL 04515/0151**

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	
Product Information Leaflet	
Labelling	

**VINORELBINE 10MG/ML STERILE CONCENTRATE
PL 04515/0151**

LAY SUMMARY

The MHRA today granted Mayne Pharma Plc a Marketing Authorisation (licence) for the medicinal product Vinorelbine 10mg/ml Sterile Concentrate (PL 04515/0151). This is a prescription only medicine (POM) for the first-line treatment of Stage 3 or 4 non-small cell lung cancer or treatment of advanced breast cancer Stage 3 and 4 in patients who have not responded to certain other anti-cancer drugs."

Vinorelbine 10mg/ml Sterile Concentrate contains the active ingredient vinorelbine tartrate, which causes cancer cells to die.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Vinorelbine 10mg/ml Sterile Concentrate outweighed the risks, hence a Marketing Authorisation has been granted.

**VINORELBINE 10MG/ML STERILE CONCENTRATE
PL 04515/0151**

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction	Page 4
Pharmaceutical assessment	Page 5
Preclinical assessment	Page 7
Clinical assessment (including statistical assessment)	Page 8
Overall conclusions and risk benefit assessment	Page 11

INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a marketing authorisation for the medicinal product Vinorelbine 10mg/ml Sterile Concentrate to Mayne Pharma Plc (PL 04515/0151) on 23rd January 2006. The product is a prescription only medicine.

The application was submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, claiming essential similarity to the original product Navelbine 10mg/ml Injectable Solution For Intravenous Infusion (Pierre Fabre Limited, UK).

The product contains the active ingredient vinorelbine tartrate and is indicated for the first-line treatment of Stage 3 or 4 non-small cell lung cancer or treatment of advanced breast cancer Stage 3 and 4 relapsing after, or refractory to, an anthracycline containing regimen.

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.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

RINN	Vinorelbine tartrate
Chemical Name:	Methyl (3aR,4R,5S,5aR,10bR,13aR)-4-(acetyloxy)-3a-ethyl-9[(8S)-4-ethyl-8-(methoxycarbonyl)-1,3,6,7,8,9-hexahydro-2H-methanoazacyclodecino[4,3-b]indol-8-yl]-5-hydroxy-8-methoxy-6-methyl-3a,4,5,5a,6,11,12,13a-octahydro-1H-indolizino[8,1-cd]carbazol-5-carboxylate (2R,3S)-2,3-dihydroxybutanedioate
	Or: 3',4'-Didehydro-4'-deoxy-8'-norvincal leukoblastine ditartrate
Formula:	$C_{45}H_{54}N_4O_8 \cdot 2(C_4H_6)_6$
RMM:	1079.11
General properties:	White to almost white powder which is hygroscopic. Freely soluble in water and alcohol; practically insoluble in hexane.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis. No materials of animal or human origin are used in the production of the active substance.

An appropriate specification is provided for the active substance vinorelbine tartrate.

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

Appropriate proof of structure has been supplied for the active pharmaceutical ingredient.

All potential known impurities have been identified and characterised.

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

The container used for storage of the active substance is satisfactory.

Appropriate stability data have been generated and no indication of instability seen. The data support a retest period of 12 months when active is stored at -20°C.

DRUG PRODUCT

Other ingredients

Other ingredients consisted of pharmaceutical excipients water for injections (diluent) and nitrogen (for deoxygenation of water for injections and for the headspace gas in the vials). All excipients used comply with their respective Ph Eur monograph. Satisfactory certificates

of analysis have been provided for all excipients. None of the excipients used contain material of animal or human origin.

Essential similarity

The physico-chemical properties of the drug product have been compared with the originator product. Essential similarity has been adequately demonstrated.

Manufacture

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

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on full-scale batches of the product. The results appear satisfactory.

Finished product specification

The finished product specification is satisfactory. Test methods have been described and have been adequately validated as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to Ph Eur standards.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months has been set, which is satisfactory. The precautions 'Keep container in outer carton' and 'Store in refrigerator (2-8°C)' have been included.

Conclusion

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

The requirements for essential similarity of the proposed and originator products have been met with respect to qualitative and quantitative content of the active substance. In addition, similar physico-chemical properties have been demonstrated for the proposed and originator products.

PRECLINICAL ASSESSMENT

I INTRODUCTION

Vinorelbine is a cytostatic anti-neoplastic compound of the vinca alkaloid class. In general, it is given following appropriate dilution at 25 – 30 mg/m² weekly by slow bolus or a short infusion. The maximum tolerated dose per administration is 34.4 mg/m² and the maximum total dose per administration is 60 mg, approximately 1 mg/kg depending on body weight.

No preclinical studies have been conducted. Preclinical data published in the literature have been reviewed for the non-clinical overview and generally do not make any reference to GLP. Hence, compliance with the regulations cannot be verified and it is recognised that the studies reviewed do not correspond to those normally conducted in support of a regulatory submission.

II PHARMACODYNAMICS

The mechanism of action of vinorelbine is mediated through a biochemical interaction. It binds to tubulin in the mitotic spindle apparatus, causing faulty cell division during mitosis and consequent lethality in rapidly dividing cells. Vinorelbine has been found to be active in cancer cell-lines either native to or xenografted into mice as host species.

II.1 Secondary Pharmacology

In mice at doses up to 24 mg/kg intravenously, dose-dependent effects on the circadian rhythms have been found, relating to temperature control, locomotor activity and rest/activity control. The degree of toxicity in mice has also been found to depend of the time of dosing. Clinical experience indicates that there is no such problem in therapeutic use.

None of the papers reviewed addresses the question of general safety pharmacology for vinorelbine in animals but, since the common adverse reactions in patients do not suggest any specific pharmacological effects, this is considered acceptable.

There is no information on possible interactions between vinorelbine and potential concomitant medications, but it is argued that the nature of the pharmacodynamic effect suggests that there is little potential for pharmacologically-based interactions.

III PHARMACOKINETICS / TOXICOKINETICS

The nonclinical overview also contains a summary of human plasma kinetics, and it is concluded that the kinetics in animals and humans are similar.

III.1 Absorption

The product is designed for parenteral administration.

III.2 Distribution

Following intravenous administration in rats, tissue distribution of vinorelbine-related material was widespread and rapid.

In rats, vinorelbine has been found to cross the placenta.

Vinorelbine is carried in the blood by α -1-acid glycoprotein but in humans, binding to albumin, globulin and lipoproteins is less than that to platelets and lymphocytes. The free fraction is 1.8%. In rats, *in vivo* plasma protein-binding was found to be concentration-dependent with 81.8% binding at 51.6 ng.equ/ml and 92.2% at 15.1 ng.equ/ml.

III.3 Metabolism

The only animal species for which there is information in the literature are the mouse and the micro-pig. In the former, a major pathway is deacetylation but in the latter, the excretion in the bile of a deacetylated metabolite was low and inconsistent.

In humans, twenty-five percent of an intravenous dose was excreted unchanged and urinary elimination accounted for eleven percent of the dose, small amounts of which consisted of the desacetyl metabolite. Other metabolites have been proposed based on theoretical considerations but have not been characterised.

Because of the scant information in both animals and humans, inter-species comparisons cannot be drawn, but given the clinical experience with the drug, this is acceptable.

III.4 Excretion

In mice, clearance occurs in the liver with elimination via the bile and to a lesser extent in the urine (79% and 10% respectively). Part of the material in both routes consisted of the deacetylated metabolite. In rats, the corresponding figures were 71.3% and 15.5% and in dogs 76.9% and 10.6%.

The pattern of excretion in the animal species is similar to that in the human, i.e. the majority of drug-related material being eliminated in the bile and a smaller amount in the urine. Despite the absence of detailed information on the nature of the metabolites, the similarity in the distribution and excretion between animals and humans provides reassurance that animals handle the material similarly to humans and that toxicity data are valid.

IV PHARMACOKINETIC DRUG INTERACTIONS

There are no data in animals presented in the nonclinical overview. It is noted that vinorelbine is metabolised by cytochrome P₄₅₀ (CYP) 3A4 in humans and some slight inhibition of CYPs 2D6, 2C8/9 and 2C19 occurs.

The proposed SPC contains a list of interactions relevant to clinical use but does not make specific mention of possibility of competition for CYP₄₅₀ 3A4 mentioned in the nonclinical overview.

V TOXICOLOGY

V.1 Acute toxicity

The LD₅₀ for vinorelbine bitartrate in C57BL/6 mice by the intravenous route was estimated to be 28 mg/kg. In CD2F mice, the LD₁₀ was 16.2 mg/kg and a dose of 24 mg/kg was lethal to all the animals tested.

V.2 Repeat-dose toxicity

There were no references on repeat-dose toxicity found in the literature.

Other information indicates that the main toxic effect of vinorelbine is leucopaenia.

In rats and dogs, elevated plasma levels of liver transaminases were found in studies with dosing regimens varying between one to five times weekly and for nine to twenty-six weeks' duration.

V.3 Reproductive toxicity

A study to detect embryo-fetal toxicity was reviewed.

Vinorelbine ditartrate was administered to rats at doses up to 0.5 mg/kg on days 7, 10, 13 and 16 of gestation. There were no effects on the general condition or physical signs in the adult females either during gestation or lactation. There were no effects on the general condition and growth of the litters during lactation nor on the selected F₁ animals up to eleven weeks of age, with the exception of a reduction in rearing in the open field test in males and females at 0.5 mg/kg. Fertility of F₁ animals was slightly reduced at 0.22 and 0.5 mg/kg. It was concluded that there were no significant toxic effects and the responses at higher doses were consistent with the action of the drug.

Fetuses from this study were also examined for visceral and skeletal abnormalities and for post-natal physical development. There were no effects on morphology up to 0.22 mg/kg, and none on post-natal development to weaning at 0.5 mg/kg. There were some vertebral and rib abnormalities occurring at 0.5 mg/kg that were considered to be treatment-related.

The overall conclusion is that vinorelbine is a possible teratogen. The dose at which the skeletal abnormalities were found (0.5 mg/kg) was half the potential human dose (1 mg/kg).

The product is contra-indicated during pregnancy and it is not known if it is excreted in breast milk.

V.4 Genotoxicity

Vinorelbine at 0.5 mg/l arrested cell division but did not increase the rate of sister chromatid exchange (SCE) in Chinese hamster ovary (CHO) cells. Lower concentrations (down to 0.05 mg/l) produced an increased incidence of abnormal anaphase responses, including lagging chromosomes and multi-polar spindles. It was concluded that vinorelbine acts on spindle microtubules, thereby altering chromosome movement and causing aneuploidies.

In haematopoietic cells, vinorelbine at 0.02 mg/l inhibited colony formation of the progenitor cells and produced myelotoxicity in murine bone marrow. At 0.025 mg/l, there were no effects on stromal cells but higher concentrations (not specified) produced loss of cellularity in the stromal layer.

V.5 Carcinogenicity

There are no studies available for review. However, the genotoxicity data indicate that there is a theoretical potential for vinorelbine to produce viable aneuploidic cells that could become the source of neoplasia.

V.6 Local tolerance

There are no non-clinical local tolerance studies. Given the extent of clinical experience with vinorelbine, this is acceptable.

V.7 Impurities

A discussion of the impurities is presented, showing that all were present at levels below that requiring qualification.

V.8 Excipients

The only excipient is water for injection.

V.9 Environmental Risk Assessment

The applicant has not carried out an environmental risk assessment, on the grounds that the application is for a product intended to be used in place of one already on the market, and claims a categorical exclusion. The SPC contains adequate instructions regarding disposal of the product.

Assessor's comment

The non-clinical overview consists of very brief overview of twenty-nine references, with no narrative summaries included. However, appropriate consideration is given to any deficiencies in the data, such as absence of data on metabolites. There is no repeat-dose toxicity data as such, but since this has been superseded by clinical data, it is acceptable.

There is a small amount of data on reproductive and genetic toxicity and a theoretical risk of the potential for carcinogenicity is recognised.

The product is intended to be used in the same way as Navelbine® 10mg/ml injectable solution, currently on the UK market, and it is considered that there is no potential risk to human health from the Mayne product over and above those already known for Navelbine® 10mg/ml injectable solution.

VI NON-CLINICAL OVERVIEW

The non-clinical overview provided is satisfactory.

VII SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

This is satisfactory.

VIII CONCLUSION

This application has not revealed any evidence of potential risks to human health from treatment with Vinorelbine 10 mg/ml Sterile Concentrate beyond the already well-described effects of vinorelbine and adequate warnings are proposed. There is no objection to the grant of a licence from a preclinical point of view.

CLINICAL ASSESSMENT

1. INDICATIONS

As a single agent, or in combination with other agents, 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.

2. DOSE & DOSE SCHEDULE

The dose and dose schedule is consistent with that for the UK reference product.

3. TOXICOLOGY

No formal data is provided under this heading and none are required for this application.

There is a non-clinical overview written by a consultant to the pharmaceutical industry. He concludes that non-clinical data has been superseded by human data and of relatively little importance in the assessment of the safe use of this agent.

4. CLINICAL PHARMACOLOGY

This application does not require the inclusion of a bioequivalence study as it is an application claiming essential similarity for a parenteral drug containing the same active substance in the same concentration as the reference product.

5. EFFICACY

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

6. SAFETY

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

7. CLINICAL OVERVIEW

There is a clinical overview from a consultant to the pharmaceutical industry. He concludes that vinorelbine can therefore be regarded as having a favourable benefit/risk balance.

8. SUMMARY OF PRODUCT CHARACTERISTICS

This is consistent with the summary of product characteristics for the reference product.

9. PATIENT INFORMATION LEAFLET

This is satisfactory.

10. LABELLING

This is satisfactory.

11. DISCUSSION

The data presented has shown that vinorelbine sterile concentrate 10 mg/ml is essentially similar to Navelbine 10 mg/ml solution for infusion.

12. RECOMMENDATIONS

The efficacy and safety of the product are satisfactory for the grant of a product licence.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Vinorelbine 10mg/ml Sterile Concentrate 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 studies were conducted. The preclinical data submitted have not revealed any evidence of potential risks to human health from treatment with Vinorelbine 10 mg/ml Sterile Concentrate beyond the already well-described effects of vinorelbine.

EFFICACY

No new or unexpected safety concerns arise from this application.

The SPC and PIL are satisfactory and consistent with that for the reference products.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with vinorelbine is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

**VINORELBINE 10MG/ML STERILE CONCENTRATE
PL 04515/0151**

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 5 th September 2003
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 21 st October 2003
3	The application went before the Committee on Safety of Medicines (CSM) on 29 th April 2004 and advice of the CSM findings were sent to the applicant on 10 th May 2004
4	Additional clinical and pharmaceutical information was provided in June 2004 and further pharmaceutical information in October 2004
5	Additional pharmaceutical information was requested from the applicant on 18 th February 2005, 10 th June 2005 and 23 rd June 2005.
6.	Additional pharmaceutical information was provided and the applications were determined on 23 rd January 2006.

**VINORELBINE 10MG/ML STERILE CONCENTRATE
PL 04515/0151**

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vinorelbine 10 mg/ml Sterile Concentrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vinorelbine (as tartrate) 10mg/ml

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

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

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion

A clear, colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

As a single agent, or in combination with other agents, for the first line treatment of stage 3 or 4 non-small cell lung cancer.

Treatment of advanced breast cancer stage 3 and 4 relapsing after, or refractory to, an anthracycline containing regimen.

4.2 Posology and method of administration

Strictly by intravenous infusion through an infusion line. Administration by other routes is fatal.

Administration should always be followed by a saline 0.9% infusion to flush the vein.

It is extremely important to make sure that the needle is correctly inserted into the vein before commencing the injection (see 4.4).

In adults:

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

Vinorelbine may be administered by slow bolus (5-10 minutes) after dilution in 20-50 ml of saline 0.9% or dextrose 5%, or by a short infusion (20-30 minutes) after dilution in 125 ml of saline 0.9% or dextrose 5%.

The maximum tolerated dose per administration : 35.4 mg/m²

The maximum total dose per administration : 60 mg

Impaired renal function:

There is no pharmacokinetic rationale for reducing the dose of vinorelbine in patients with impaired renal function.

Impaired hepatic function:

Doses of vinorelbine should be reduced and the drug should be administered with caution in patients with hepatic impairment. One dosage regime described in literature suggests dosing as follows: patients with total serum bilirubin concentration of $34\mu\text{mol/l}$ or less, no dosage reduction; patients with total serum bilirubin concentration of $35 - 50\mu\text{mol/l}$, vinorelbine dose should be reduced to 15 mg/m^2 ; patients with total serum bilirubin concentration exceeding $50\mu\text{mol/l}$, vinorelbine dose should be reduced to 7.5 mg/m^2 .

In patients with massive liver metastases (i.e. $> 75\%$ of liver volume replaced by the tumour), it is empirically suggested that the dose be reduced by $1/3$ and the haematological toxicity closely followed-up.

The dose limiting toxicity of vinorelbine is mainly neutropenia. This usually occurs between day 8 and day 12 after drug administration, is short-lived, and is not cumulative. If the neutrophil count is $< 2000/\text{mm}^3$ and/or platelet number is $< 75000/\text{mm}^3$, then the treatment should be delayed until recovery. Drug administration is expected to be delayed by 1 week in about 35% of treatment courses.

Elderly:

Studies of patients aged above 65 have not shown any significant differences in efficacy or safety. Nevertheless, geriatric patients present a greater risk of myelosuppression and cardiotoxicity with the use of antineoplastic agents in general. In addition, due to the slow destruction of the haemato-encephalic barrier, effects are more frequent on the central nervous system. Use with caution.

Children:

The safety and efficacy of the use of vinorelbine in children has not been established.

4.3 Contraindications

Pregnancy and lactation

Severe hepatic insufficiency not related to the tumoural process.

History of allergic reaction to vinorelbine or other vinca alkaloids.

4.4 Special warnings and special precautions for use

Vinorelbine must always only be administered by the intravenous route.

Administration by other routes is fatal. Administration should always be followed by a normal saline infusion to flush the vein.

It is extremely important to make sure that the needle is correctly inserted into the vein before commencing the injection. In the event of extravasation, cellulitis or even necrosis could occur. The injection should be immediately stopped and the maximum amount of product extravasated should be removed; the remaining amount should be administered into another vein.

Vinorelbine may only be used under the strict control of a doctor specialising in the use of oncological chemotherapeutics, preferably in institutions in which the staff have experience of such therapies.

Close haematological checks are necessary during treatment (measurement of haemoglobin level, leucocyte, granulocyte and thrombocyte counts before each administration plus routine checking of hepatic and renal laboratory parameters

(especially if administered simultaneously with cisplatin) and of serum electrolytes). In neutropenia ($<2,000/\text{mm}^3$) or thrombocytopenia ($<100,000/\text{mm}^3$) the patient must be kept under observation 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.

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

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

Neurological examinations must be carried out in long term treatment with vinorelbine and in patients at a high risk, such as those with pre-existing neuropathy.

Vinorelbine should not be given concomitantly with radiotherapy if the treatment field includes the liver. No irradiation of the pelvis, the spine or the hollow bones should be carried out simultaneously with the administration of vinorelbine, as elevated myelotoxicity can be expected in this case. The same applies to previous radiation treatment (<3 weeks) of the same regions.

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 saline 0.9% should be undertaken if any contact occurs.

Contraceptive measures must be taken by both men and women during treatment and for three months after treatment has been discontinued.

4.5 Interaction with other medicinal products and other forms of interaction

The combination vinorelbine-cisplatin shows no interaction with respect to the pharmacokinetic parameters. However, a higher incidence of grade 3 and 4 granulocytopenia has been reported in patients receiving combination therapy with vinorelbine and cisplatin than in those receiving vinorelbine alone.

The combination of high dose vinorelbine with mitomycin C appears to lead to signs of elevated pulmonary toxicity (bronchospasms, breathlessness) in isolated cases, for which an allergic genesis is under discussion. As mitomycin C also occasionally enhances the potential pulmonary toxicity of other vinca alkaloids, particular caution is advised in the simultaneous use of vinorelbine and mitomycin C in patients with an allergic predisposition (bronchial asthma, known allergies).

The combination of vinorelbine and gemcitabine may have serious hepatic risks which can be fatal.

Vinorelbine is metabolised by CYP3A4. Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes CYP 3A4 subfamily, or other CYP3A substrates. Concomitant administration with other CYP3A4 substrates may result in increased serum levels and therefore increased toxicity of vinorelbine and other CYP3A4 substrates.

The following interactions have not been reported specifically with vinorelbine, however, they have been reported with other vinca alkaloids, and therefore caution is advised:

- phenytoin (introduced to treat the convulsive effect of certain anti-cancer drugs); risk of occurrence of convulsions through reduced digestive absorption of phenytoin by the cytostatic.
- vaccine against yellow fever; risk of generalised fatal vaccine disease.
- live vaccines; risk of generalised vaccine disease, possibly fatal. This risk is increased in subjects already immuno-depressed by the underlying disease. Use a non-living vaccine if possible.
- ciclosporin; excessive immuno-depression with risk of lympho-proliferation.
- tacrolimus; excessive immuno-depression with risk of lympho-proliferation.
- itraconazole; increase in neurotoxicity of the antimetabolic by reduction of its liver metabolism.

4.6 **Pregnancy and lactation**

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

Women should not become pregnant during treatment with vinorelbine.

This product should not be used during pregnancy.

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

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

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

None known.

4.8 **Undesirable effects**

Endocrine disorders

There have been rare reports of inappropriate antidiuretic hormone secretion (SIADH)

Blood and lymphatic system disorders

The limiting toxicity is neutropenia (G1 : 9.7%; G2 : 15.2%; G3 : 24.3%; G4 : 27.8%) which is rapidly reversible and non-cumulative. Further treatment may be given after recovery of the granulocyte count.

Anaemia (G1-2 : 61.2%; G3-4 : 7.4%) and thrombocytopenia (G1-2 : 5.1%; G3-4 : 2.5%) are seldom severe.

Nervous system disorders

Peripheral - This is generally limited to loss of deep tendon reflexes; severe paraesthesia are uncommon (G1 : 17.2%; G2 : 3.6%; G3 : 2.6%; G4 : 0.1%). The effects are dose dependent but reversible when treatment is discontinued.

Autonomic neuropathy – The main symptom is intestinal paresis causing constipation (G1 : 16.9%; G2 : 4.9%) which rarely progresses to paralytic ileus (G3 : 2%; G4 : 0.7%). Treatment may be resumed after recovery of normal bowel mobility.

Cardiac disorders

There have been rare reports of cardiac ischaemia (reversible ECG changes, angina pectoris or myocardial infarct).

As with other vinca alkaloids, vinorelbine may occasionally produce dyspnoea.

Respiratory, thoracic and mediastinal disorders

As with other vinca alkaloids vinorelbine may incur bronchial spasms immediately after injection, but this may also be observed some hours later.

There have been rare reports of interstitial lung disease, especially in patients who are given a combination of vinorelbine and mitomycin. There is a single case in which acute respiratory failure, while vinorelbine was being administered with a fatal outcome was observed after previous radiation treatment.

Gastrointestinal disorders

Constipation (see autonomic neuropathy)

Diarrhoea (G1 : 7.6%; G2 : 3.6%; G3 : 0.7%; G4 : 0.1%) : severe diarrhoea is uncommon.

Nausea-vomiting (G1 : 19.9%; G2 : 8.3%; G3 : 1.9%; G4 : 0.3%) : severe nausea and vomiting may occasionally occur. Conventional anti-emetic therapy reduces these undesirable effects.

Skin and subcutaneous tissue disorders

Alopecia is mild but may appear progressively with extended courses of treatment (G1-2 : 21%; G3-4 : 4.1%)

Musculoskeletal, connective tissue and bone disorders

Jaw pain has occasionally been reported.

General disorders and administration site conditions

Allergic type reactions have been reported

Burning pain at the injection site and local phlebitis (G1 : 12.3%; G2 : 8.2%; G3 : 3.6%; G4 : 0.1%) may be observed with repeated injections of vinorelbine.

Bolus injection followed by liberal flushing of the vein (saline 0.9% is recommended) can limit this effect. Insertion of a central venous line may be necessary.

Any extravasation may induce local reactions which rarely progress to necrosis. (See 4.2 posology and method of administration).

4.9 Overdose

In studies of acute toxicity in animals the symptoms of overdose were: pilo erection, behaviour abnormalities (lethargy, prostration), pulmonary lesions, weight loss and bone marrow hypoplasia.

Accidental overdosages have been reported in humans. They may produce a period of bone marrow aplasia sometimes associated with fever, infection and possibly paralytic ileus. Management of the infectious complications is by broad-spectrum antibiotic therapy and the paralytic ileus is managed by naso-gastric aspiration.

As no known specific antidote is known, symptomatic measures are required in every overdose. These measures include:

- Continuous checks of vital signs and especially careful monitoring of the patient.
- Daily blood count in order to detect the need for transfusion, and to estimate the infection risk and the need for intensive medical care.

- Monitoring of the cardiovascular system
- Checks on liver function.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: LO1C A04

Vinorelbine is a cytostatic antineoplastic drug of the vinca alkaloid family with a molecular action on the dynamic equilibrium of tubulin in the microtubular apparatus of the cell. It inhibits tubulin polymerisation and binds preferentially to mitotic microtubules, only affecting axonal microtubules at high concentration. The induction of tubulin spiralization is less than that produced by vincristine. Vinorelbine blocks mitosis at G2-M, causing cell death in interphase or at the following mitosis.

5.2 Pharmacokinetic properties

After intravenous administration of vinorelbine 30 mg/m² in patients, the plasma concentration of the active ingredient is characterised by a three exponential elimination curve. The end-elimination phase reflects a long half-life greater than 40 hours. Total clearance of vinorelbine is high (1.3 l/h/kg) with excretion occurring mainly by the biliary route; renal excretion is minimal (18.5% of label is recovered in urine).

The active ingredient is widely distributed in the body with a volume of distribution greater than 40 l/kg. There is moderate binding to plasma proteins (13.5%), but strong binding to platelets (78%). Penetration of vinorelbine into pulmonary tissue is significant with tissue/plasma concentration ratios of greater than 300 in a study involving surgical biopsy.

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

5.3 Preclinical safety data

Mutagenic and carcinogenic potential

The interaction of vinorelbine with the spindle apparatus during mitosis can cause an incorrect distribution of chromosomes. In animal studies vinorelbine induced aneuploidy and polyploidy. It is therefore to be assumed that vinorelbine can also cause mutagenic effects (induction of aneuploidy) in man.

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 fetolethal 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 IV, 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.

In haemodynamic and electrocardiographic studies on animals, no haemodynamic effects have been found using a maximal tolerated dose in dogs, however only some non significant disturbances of repolarization were found for all vinca alkaloids tested. No effect on the cardiovascular system has been detected using repeated doses (study 39 weeks) of vinorelbine on primates.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injections

6.2 Incompatibilities

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

In case of polychemotherapy, vinorelbine should not be mixed with other agents.

Vinorelbine is not adsorbed to or affected by either PVC, polypropylene or clear neutral glass. (See 6.2, in use shelf-life).

6.3 Shelf life

Prior to first use: 24 months

In use: Following dilution in saline 0.9% or dextrose 5%, chemical and physical in-use stability has been demonstrated for up to 8 days at 2-8°C in PVC infusion bags and polypropylene syringes. From a microbiological point of view, however, 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 when stored at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions

6.4 Special precautions for storage

Prior to first use: Store at 2-8°C. Keep container in the outer carton.

In use: See section 6.3

6.5 Nature and contents of container

10 mg/1 ml – 2 ml clear Type I glass vials and ONCO-TAIN[®] vials with rubber closures, packed as single vials or packs of 10.

50 mg/5 ml - 5 ml clear Type I glass vials and ONCO-TAIN[®] vials with rubber closures, packed as single vials or packs of 10.

6.6 Instructions for use and handling

Single use only. Discard any unused contents.

Vinorelbine may have a pale yellow colouration which does not affect the quality of the product.

Handling guidelines

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

Preparation of solution for administration should be carried out in a designated handling area and working over a washable tray or disposable plastic-backed absorbent paper.

Suitable eye protection, disposable gloves, face mask and disposable apron should be worn.

Syringes and infusion sets should be assembled carefully to avoid leakage (use of Luer lock fittings is recommended).

Actual spillage or leakage should be mopped up wearing protective gloves.

All contact with the eye should be strictly avoided; risk of severe irritation and even corneal ulceration if the drug is sprayed under pressure. Immediate liberal washing of the eye with saline 0.9% should be undertaken if any contact occurs.

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

Disposal guidelines

All sharps should be placed in an appropriate container and all other disposable items and cleaning materials in a sealed plastic bag which should be incinerated with other clinical waste.

Waste material may be disposed of by incineration.

7. MARKETING AUTHORISATION HOLDER

Mayne Pharma Plc
Queensway
Royal Leamington Spa
Warwickshire CV31 3RW
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 04515/0151

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/01/2006

10. DATE OF REVISION OF THE TEXT

23/01/2006

6/2005 10:46 AM Page 1 (1, 1)

TECHNICAL LEAFLET**DBL®****Vinorelbine 10 mg/ml Sterile Concentrate**

This is an extract from the Summary of Product Characteristics (SmPC) to assist in the administration of Vinorelbine 10 mg/ml Sterile Concentrate. When determining appropriateness of use in a particular patient, the prescriber should be familiar with the full SmPC. You should be experienced in the handling and use of cytotoxic agents. Reference should be made to local policy guidelines on the safe handling of cytotoxic agents.

Route of administration

Strictly by intravenous infusion through an infusion line. Administration by other routes is fatal.

Must be diluted before use.

Incompatibilities

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

In case of polychemotherapy, vinorelbine should not be mixed with other agents.

Vinorelbine is not adsorbed to or affected by either PVC, polypropylene or clear neutral glass.

Preparation Instructions

This is a cytotoxic product, please follow your local policy guidelines for instructions on the safe handling/destruction of cytotoxics and refer to the section on use and handling at the end of this leaflet.

Vinorelbine may be administered after dilution in saline 0.9% or dextrose 5%.

The volume of diluent depends on the mode of administration:

bolus = 20-50 ml

infusion = 125 ml

Vinorelbine must be given strictly intravenously. It is extremely important to make sure that the needle is correctly inserted into the vein before commencing the injection.

Dosage and Administration**In adults:**

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

2005-10-16 AM Page 1 (1, 2)

Dosage and Administration**In adults:**

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

Vinorelbine may be administered by slow bolus (over 5-10 minutes) after dilution in 20-50 ml of saline 0.9% or dextrose 5%, or by a short infusion (over 20-30 minutes) after dilution in 125 ml of saline 0.9% or dextrose 5%. Administration should always be followed by a saline 0.9% infusion to flush the vein.

The maximum tolerated dose per administration : 35.4 mg/m²

The maximum total dose per administration : 60 mg

Impaired renal function:

There is no pharmacokinetic rationale for reducing the dose of vinorelbine in patients with impaired renal function.

Impaired hepatic function:

Doses of vinorelbine should be reduced and the drug should be administered with caution in patients with hepatic impairment. One dosage regime described in literature suggests dosing as follows: patients with total serum bilirubin concentration of 34 µmol/l or less, no dosage reduction; patients with total serum bilirubin concentration of 35-50 µmol/l, vinorelbine dose should be reduced to 15 mg/m²; patients with total serum bilirubin concentration exceeding 50 µmol/l, vinorelbine dose should be reduced to 7.5 mg/m².

In patients with massive liver metastases (i.e. > 75% of liver volume replaced by the tumour), it is empirically suggested that the dose be reduced by 1/3 and the haematological toxicity closely followed-up.

The dose limiting toxicity of vinorelbine is mainly neutropenia. This usually occurs between day 8 and day 12 after drug administration, is short-lived, and is not cumulative. If the neutrophil count is < 2000/mm³ and/or platelet number is < 75000/mm³, then the treatment should be delayed until recovery. Drug administration is expected to be delayed by 1 week in about 35% of treatment courses.

Elderly:

Studies of patients aged above 65 have not shown any significant differences in efficacy or safety. Nevertheless, geriatric patients present a greater risk of myelosuppression and cardiotoxicity with the use of antineoplastic agents in general. In addition, due to the slow destruction of the haemato-encephalic barrier, effects are more frequent on the central nervous system. Use with caution.

Children:

The safety and efficacy of the use of vinorelbine in children has not been established.

Warnings

Vinorelbine must always be administered by the intravenous route. Administration by other routes is fatal. Administration should always be followed by a normal saline infusion to flush the vein.

Please tear here

Please tear here

PATIENT INFORMATION LEAFLET

This leaflet contains important information about your medicine; read it carefully.

Keep this leaflet; you may want to read it again.

If you have any questions or are not sure about anything, ask your doctor or pharmacist.

Vinorelbine 10 mg/ml Sterile Concentrate

- The active substance is vinorelbine (as tartrate)
- The other ingredient is Water for Injections

The marketing authorisation holder and company responsible for batch release in the European Union is Mayne Pharma Plc, Queensway, Royal Leamington Spa, Warwickshire, CV31 3RW, United Kingdom.

The manufacturer is Mayne Pharma Pty Ltd, Lexia Place, Mulgrave, Victoria 3170, Australia.

1. What Vinorelbine Sterile Concentrate is and what it is used for

Vinorelbine Sterile Concentrate is an anti-cancer medicine, in the form of a concentrate for solution for infusion (concentrated solution which is diluted to make a solution which can be given as a slow injection via a drip). Treatment with an anti-cancer medicine is often called cancer chemotherapy.

The medicine is presented in glass containers called vials. Each millilitre (ml) of Vinorelbine Sterile Concentrate contains vinorelbine tartrate equivalent to 10 milligrams (mg) of vinorelbine. Each 1 ml vial contains vinorelbine tartrate equivalent to 10 mg of vinorelbine and each 5 ml vial contains vinorelbine tartrate equivalent to 50 mg of vinorelbine. It is available in packs containing 1 vial or packs containing 10 vials. Not all pack sizes and presentations mentioned may be marketed.

Vinorelbine Sterile Concentrate is used in the treatment of lung and breast cancer.

6/2005 10:46 AM Page 2 (1, 1)

It is extremely important to make sure that the needle is correctly inserted into the vein before commencing the injection. In the event of extravasation, cellulitis or even necrosis could occur. The injection should be immediately stopped and the maximum amount of product extravasated should be removed; the remaining amount should be administered into another vein.

Vinorelbine may only be used under the strict control of a doctor specialising in the use of oncological chemotherapeutics, preferably in institutions in which the staff have experience of such therapies.

Close haematological checks are necessary during treatment (measurement of haemoglobin level, leucocyte, granulocyte and thrombocyte counts before each administration plus routine checking of hepatic and renal laboratory parameters (especially if administered simultaneously with cisplatin) and of serum electrolytes). In neutropenia ($< 2,000/\text{mm}^3$) or thrombocytopenia ($< 100,000/\text{mm}^3$) the patient must be kept under observation 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.

Vinorelbine should not be given concomitantly with radiotherapy if the treatment field includes the liver. No irradiation of the pelvis, the spine or the hollow bones should be carried out simultaneously with the administration of vinorelbine, as elevated myelotoxicity can be expected in this case. The same applies to previous radiation treatment (< 3 weeks) of the same regions.

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 saline 0.9% should be undertaken if any contact occurs.

Overdose

Accidental overdosages have been reported in humans. They may produce a period of bone marrow aplasia sometimes associated with fever, infection and possibly paralytic ileus. Management of the infectious complications is by broad-spectrum antibiotic therapy and the paralytic ileus is managed by naso-gastric aspiration.

As no known specific antidote is known, symptomatic measures are required in every overdose. These measures include:

- Continuous checks of vital signs and especially careful monitoring of the patient.
- Daily blood count in order to detect the need for transfusion, and to estimate the infection risk and the need for intensive medical care.
- Monitoring of the cardiovascular system.
- Checks of liver function.

Use and Handling

Single use only. Discard any unused contents.

Vinorelbine may have a pale yellow colouration which does not affect the quality

• Checks of liver function.
6/2005 10:46 AM Page 2 (1, 2)

Use and Handling

Single use only. Discard any unused contents.

Vinorelbine may have a pale yellow colouration which does not affect the quality of the product.

Handling guidelines

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

Preparation of solution for administration should be carried out in a designated handling area and working over a washable tray or disposable plastic-backed absorbent paper.

Suitable eye protection, disposable gloves, face mask and disposable apron should be worn.

Syringes and infusion sets should be assembled carefully to avoid leakage (use of Luer lock fittings is recommended).

Actual spillage or leakage should be mopped up wearing protective gloves.

All contact with the eye should be strictly avoided; risk of severe irritation and even corneal ulceration if the drug is sprayed under pressure. Immediate liberal washing of the eye with saline 0.9% should be undertaken if any contact occurs.

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

Disposal guidelines

All sharps should be placed in an appropriate container and all other disposable items and cleaning materials in a sealed plastic bag which should be incinerated with other clinical waste.

Waste material may be disposed of by incineration.

Storage

Store at 2-8°C. Keep container in the outer carton.

Following dilution in saline 0.9% or dextrose 5%, chemical and physical in-use stability has been demonstrated for up to 8 days at 2-8°C in PVC infusion bags and polypropylene syringes.

From a microbiological point of view, however, 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 when stored at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Marketing Authorisation Holder



Mayne Pharma Plc
Warwickshire, CV31 3RW
United Kingdom

Date of Preparation

8th June 2004

Please tear here

Please tear here

Men and women undergoing treatment with Vinorelbine Sterile Concentrate should use effective contraception during treatment and for at least 3 months after treatment has stopped.

3. How Vinorelbine Sterile Concentrate is used

The dose of Vinorelbine Sterile Concentrate that you will get is based on your body surface area, calculated from your height and your weight. The dose adults usually get is between 25-30 mg/m² weekly. However the dose will depend upon your medical condition, whether other drugs are being used at the same time, your age and the general state of your health. Your doctor will be able to explain exactly what drugs you will be given and when.

This medicine will be diluted with a solution such as saline 0.9% or dextrose 5% before it is given to you. It will be given to you as a slow injection into a vein over 5 to 10 minutes or as a slow injection via a drip into a vein over 20-30 minutes. Vinorelbine may cause death if given by a route other than the intravenous route.

It is very important that vinorelbine goes into the vein and does not leak out into the surrounding tissue. Your doctor or nurse will make sure that the needle is correctly inserted into your vein. If any leakage does occur, swelling and redness of the surrounding area may occur, or even severe or irreparable damage to the area.

It is very important that vinorelbine does not splash into the eye. If this happens it will cause severe irritation or even ulceration on the surface of the eye (corneal ulcers). If eye contact does occur, the eye will need to be washed out immediately with large amounts of saline.

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 Sterile Concentrate can have side effects.

If any of the following happen, tell the doctor immediately:

- breathing difficulties

4. **Possible side effects**
/2005 10:46 AM Page 2 (1, 3)
Like all medicines Vinorelbine Sterile Concentrate can have side effects.

If any of the following happen, tell the doctor immediately:

- breathing difficulties
- chest pain
- severe allergic reaction – you may experience a sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing), and you may feel you are going to faint.

These are very serious side effects. You may need urgent medical attention. All of these very serious side effects are rare.

If you experience any of the following tell your doctor as soon as possible:

- weakness, fatigue
- nausea and vomiting
- abnormal sensation, particularly in the hands and feet
- constipation, rarely becoming bowel obstruction, bloating
- diarrhoea
- loss of hair
- jaw pain
- swelling, soreness and/or skin rash where the injection was given
- Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH). Symptoms of this include weight gain, nausea, vomiting, muscle cramps, confusion and convulsions (fits).

Alterations in the blood may also occur, your doctor will arrange for you to have blood tests to monitor for these (low white cells, anaemia and/or low platelets and change in certain salts in your blood).

It may be necessary for you to have an examination of your nervous system.

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

5. Storing Vinorelbine Sterile Concentrate

This medicine should be kept out of reach and sight of children.

Store at 2-8°C. Following dilution in 0.9% saline or 5% dextrose, solutions should be stored at 2-8°C.


The vials should be kept in the outer carton to protect from light.

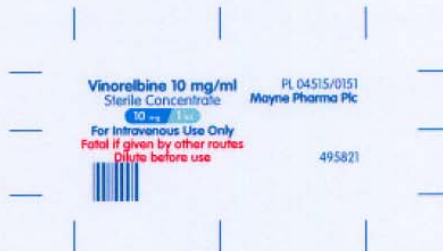
This medicine should not be used after the expiry date printed on the vial label and carton.

Date of preparation
8th June 2004

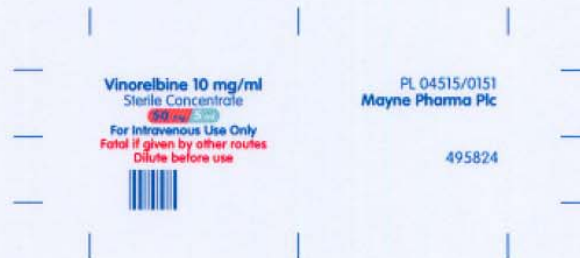
495822

version: 4
date: 14/10/04
designer: gdw

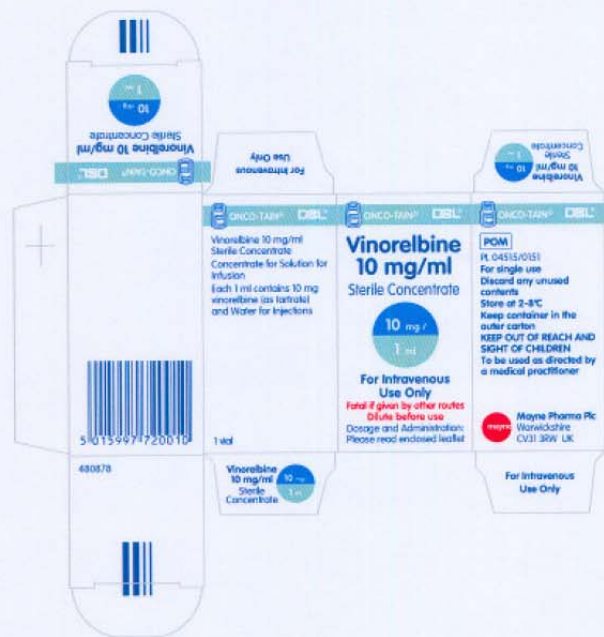
 Mayne Pharma Pty Ltd Review frequency: Three years from date of issue/review	Label specification 2 mL glass vial	Roll direction Roll in, left leading	88S081 Label size 45 x 19 mm
Container/s 461505		Stock YFilm/S692N/BG40WH	
Colour/s <ul style="list-style-type: none"> ■ 295 C Corporate blue ■ 485 C Corporate red ■ 5503 C Silver grey ■ 285 C Gee blue 	Artwork Version 3		
	Date of Preparation 12/10/04		
	Artworker/Designer gw/gdw		





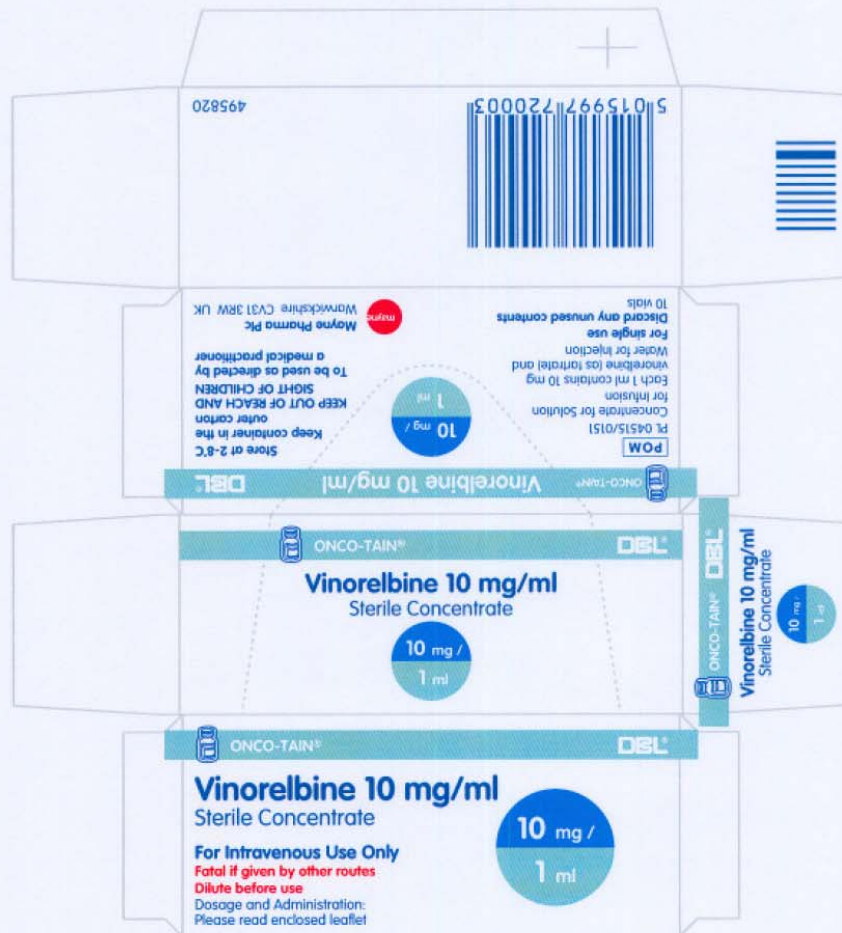
 Mayne Pharma Pty Ltd Review frequency: Three years from date of issue/review	Label specification 5 mL glass vial	Roll direction Roll in, left leading	88S082
			Label size 63 x 20 mm
Container/s 411922		Stock Mirrorkote/C58/DG7W	
Colour/s <ul style="list-style-type: none"> ■ 295 C Corporate blue ■ 485 C Corporate red ■ 5503 C Silver grey ■ 1785 C Manc red 	Artwork Version 3		
	Date of Preparation 12/10/04		
	Artworker/Designer gw/gdw		



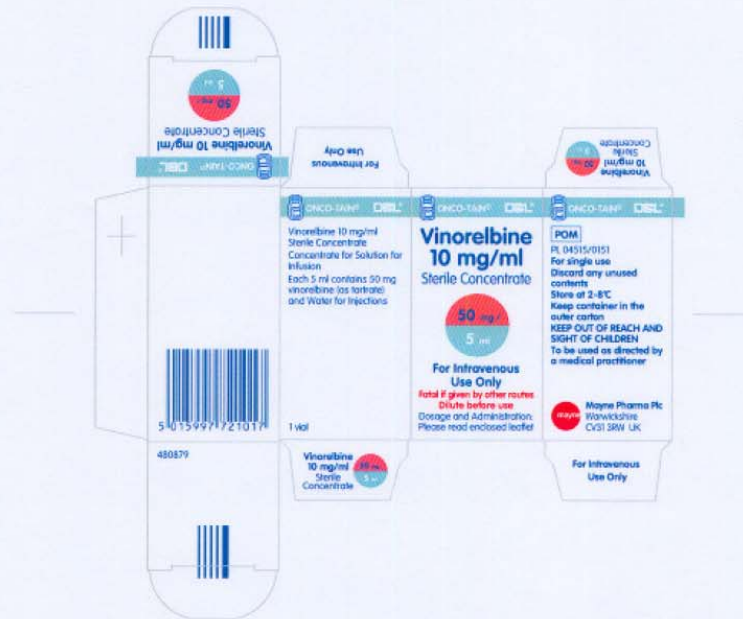
 Mayne Pharma Pty Ltd Review frequency: Three years from date of issue/review	Carton specification Various	Pack size/s 7 ml vials Single pack (A)	885018 Stock Bleetchboard 400 um
	Carton style Aeroplane tuck	Carton size 32.5 x 32.5 x 42.3 mm	
Container 461505	Artwork Version 4		
Colours/s 295 C (Corporate Blue) 485 C (Corporate Red) All text & graphics will have UV Varnish 265 C (Eye Blue) 5503 C (Silver Gray)	Date of Preparation 06/01/05		
	Artworker/Designer KJM		




 Mayne Pharma Pty Ltd Review frequency: Three years from date of issue/review	Carton specification 2 mL Vials	Pack size/s 10 pack (D) Machine packed	88S021 Stock Bleachboard 400 um
	Carton style Flap end	Carton size 34 x 38.5 x 84 mm	
Container/s 461505	Artwork Version 4		
Colour/s 295 C Corporate blue 485 C Corporate red All text & graphics will have UV Varnish 285 C Gee blue 5503 C Silver grey	Date of Preparation 12/10/04		
	Artworker/Designer gw/gdw		



 Mayne Pharma Pty Ltd Review frequency: Three years from date of issue/review	Carton specification Various	Pack size/s 5 mL vials Single pack (A)	885018 Stock Blackboard 400 um
	Carton style Aeroplane tuck	Machine/Hand packed	
Container 411922	Carton size 32.5 x 32.5 x 62.5 mm		
Colour/s 295 C (Corporate Blue) 485 C (Corporate Red) All text & graphics will have UV Varnish 5503 C (Silver Grey) 1785 C (Maric Red)	Artwork Version 4		
	Date of Preparation 06/01/05		
	Artworker/Designer KJM		



 Mayne Pharma Pty Ltd Review frequency: Three years from date of issue/review	Carton specification 5 mL Vials	Pack size/s 5 mL vial with large leaflet	885023 Stock Bleachboard 400 um
	Carton style Flap end	10 pack (D) Machine packed	
Container/s 411922	Carton size 45.5 x 45.5 x 111.5 mm		
Colour/s 295 C Corporate blue 485 C Corporate red All text & graphics will have UV Varnish 5503 C Silver grey 1785 C Manc red	Artwork Version 3		
	Date of Preparation 12/10/04		
	Artworker/Designer gw/gdw		

