

**IRISH MEDICINES BOARD ACTS 1995 AND 2006**

**MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007**

**(S.I. No.540 of 2007)**

**PA1348/016/001**

Case No: 2050861

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

**Cardinal Health UK 434 Limited**

**Bampton Road, Harold Hill, Romford, Essex RM3 8UG, United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

**Vinorelbine Martindale Pharma 10 mg/ml Concentrate for Solution for Infusion**

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **25/09/2009** until **24/09/2014**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

## Part II

### Summary of Product Characteristics

#### 1 NAME OF THE MEDICINAL PRODUCT

Vinorelbine Martindale Pharma 10 mg/ml Concentrate for Solution for Infusion

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml concentrate for solution for infusion contains vinorelbine tartrate corresponding to 10 mg vinorelbine. Each 5 ml concentrate for solution for infusion contains vinorelbine tartrate corresponding to 50 mg vinorelbine. For a full list of excipients, see section 6.1.

#### 3 PHARMACEUTICAL FORM

Concentrate for Solution for Infusion

A clear colourless solution with a pH of 3.3 to 3.8 and an osmolarity of about 47 mOsm/kg.

#### 4 CLINICAL PARTICULARS

##### 4.1 Therapeutic Indications

Vinorelbine Martindale Pharma is indicated in the treatment:

- Non-small cell lung cancer (stage 3 or 4)
- As single agent to patients with metastatic breast cancer, where treatment with anthracycline- and taxane containing chemotherapy has failed or is not appropriate.

##### 4.2 Posology and method of administration

**Strictly by intravenous injection through an infusion line after appropriate dilution.**

**The use of intrathecal route is contraindicated.**

Vinorelbine Martindale Pharma should be given with the assistance of a physician with extensive experience with therapy with cytostatics.

For instruction regarding use and handling, see section 6.6.

##### **In adults:**

Vinorelbine Martindale Pharma is usually administered at 25 – 30 mg/m<sup>2</sup> weekly.

Vinorelbine Martindale Pharma may be administered by slow bolus (5 – 10 minutes) after dilution in 20 – 50 ml of sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection or by a short infusion (20 – 30 minutes) after dilution in 125 ml of sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection. Administration should always be followed with at least 250 ml of an isotonic solution to flush the vein.

The maximum tolerated dose per administration: 35.4 mg/m<sup>2</sup> body surface area.

##### **Advanced non-small cell lung cancer:**

- In monotherapy the usual dose is 25 – 30 mg/m<sup>2</sup>, administered once weekly.

- In combination therapy, the usual dose (25 – 30 mg/m<sup>2</sup>) could be maintained, but the frequency of the administration should be reduced to for example day 1 and 5 every third week or day 1 and 8 every third week according to the treatment plan.

#### **Advanced or metastatic breast cancer:**

The usual dose is 25 – 30mg/m<sup>2</sup>, administered once weekly.

#### **Elderly:**

No dose reduction is required but a higher sensitivity to toxicity in the elderly cannot be excluded (see section 5.2: Pharmacokinetic properties)

#### **Impaired hepatic function:**

For patients presenting with severe liver impairment caution and careful monitoring of haematological parameters is recommended. The dose may have to be reduced.

See sections: 4.4: Special warnings and precautions for use  
5.2: Pharmacokinetic properties.

#### **Impaired renal function:**

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

See section 4.4: Special warnings and precautions for use.

#### **Paediatric patients:**

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

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

### **4.3 Contraindications**

Vinorelbine Martindale Pharma is contraindicated in:

- The use of the intrathecal route is contraindicated
- Known hypersensitivity to vinorelbine or to other vinca alkaloids or to any of the excipients (see section 6.1)
- Neutrophil granulocytes < 1500/mm<sup>3</sup> or serious, current or recent infection (within 2 weeks)
- Platelet count below 75,000/mm<sup>3</sup>
- Breast-feeding should be discontinued during treatment with vinorelbine (see section 4.6)
- Severe hepatic impairment not related to the tumoural process
- Women of childbearing potential not using effective contraception (see section 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.

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 1500/mm<sup>3</sup> and/or the platelet count is below 75,000/mm<sup>3</sup>, 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/m<sup>2</sup> (see section 5.3). For patients with severe hepatic impairment caution is recommended and careful monitoring of haematological parameters is required.
- Vinorelbine should not be given concomitantly with radiotherapy if the treatment plan includes the liver.
- Vinorelbine 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).
- The product is generally not recommended in combination with live attenuated vaccines.
- For information on pregnancy, breastfeeding 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 CYP3A4 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 bronchospasm (see section 4.4 and 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 required, 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.

Cyclosporine, 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 feto-lethal and teratogenic. During pregnancy this product should not be used unless clearly necessary. Fertile women should use effective methods of contraception during treatment with Vinorelbine Martindale Pharma and should inform their doctor if they are 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 also be considered.

**Breast-feeding**  
It is not known whether vinorelbine passes into breast milk. Breast-feeding must be discontinued before treatment with Vinorelbine Martindale Pharma 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.

4.8 Undesirable effects

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

Frequencies are defined as:  
very common (> 1/10), common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100), rare (> 1/10,000, < 1/1,000), very rare (< 1/10,000).

System Organ Classes (MedDRA classification)	Very common (>10)	Common (>1/100 and ≤1/10)	Uncommon (>1/1,000 and ≤ 1/100)	Rare (> 1/10,000, < 1/1,000)	Very rare (< 1/10,000)
Infections and infestations		Infection bacterial, viral or fungal at different sites, mainly due to bone marrow suppression	Severe sepsis with other visceral failure.	Septicaemia	Septicaemia complicated Septicaemia fatal
Blood and lymphatic system disorders	Neutropenia (grade 3:24.3% and grade 4:27.8% in monotherapy) Anaemia (grade 3 – 4:7.7% in monotherapy)	Thrombocytopenia (grade 3 – 4:2.5%) Febrile neutropenia Neutropenic sepsis with potential fatal outcome in 1.2%			

		of cases.			
Immune system disorders		Allergic reactions (skin reactions, respiratory reactions)		Systemic allergic reactions (anaphylaxis, angioedema)	
Metabolism and nutrition disorders		Hyponatraemia		Inappropriate antidiuretic hormone secretion (SIADH)	
Nervous system disorders	Neurological disorders (grade 3:2,6%; grade 4: 0,1%) including loss of deep tendon reflexes Constipation (grade 3-4: 2.7% in monotherapy, grade 3-4: 4.1% in combination therapy)(see also “Gastrointestinal disorders”)	Paraesthesia with sensory and motor symptoms	Paralytic ileus (see also “Gastrointestinal disorders”)	Weakness of lower extremities	Guillain-Barré syndrome
Cardiac disorders				Ischaemic heart disease such as angina pectoris Transitory electrocardiogram changes Myocardial infarction	Tachycardia Palpitation Heart rhythm disorders
Vascular disorders		Hypotension Hypertension, Flushing Peripheral coldness		Severe hypotension Collapse	
Respiratory, thoracic and mediastinal disorders		Dyspnoea Bronchospasm		Interstitial lung disease	respiratory insufficiency
Gastrointestinal disorders		Constipation (grade 3-4: 2.7% in monotherapy, grade 3-4 4.1% in combination therapy)(see also “Nervous system		Paralytic ileus (see also “Nervous system disorders”)	Pancreatitis

	disorders”) Nausea Vomiting (grade 3-4: 2.2% in monotherapy) Diarrhoea Stomatitis Oesophagitis Anorexia		
<b>Hepatobiliary disorders</b>	Abnormal liver function values (total bilirubin increased, alkaline phosphatase increased, alanine aminotransferase increased)		
<b>Skin and subcutaneous tissue disorders</b>	Alopecia (grade>2: 4.1% in monotherapy)	Skin reactions	
<b>Musculoskeletal, connective tissue and bone disorders.</b>		Arthralgia Myalgia	Jaw pain
<b>Renal and urinary disorders</b>		Creatinine increased	
<b>General disorders and administration site conditions</b>	Fatigue Fever Pain in different locations Asthenia Injection site erythema, pain, discolouration and phlebitis		Injection site necrosis

4.9 Overdose

Overdosage may result in severe bone marrow depression with fever and infection, paralytic ileus have also been reported. Symptomatic treatment with blood transfusion and broad-spectrum antibiotic therapy is recommended. There is no specific 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 minimise 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: Antineoplastic agents (vinca alkaloids)

ATC code: L01 CA04

Vinorelbine is a cytostatic drug of the vinca alkaloid family.

Vinorelbine inhibits tubulin polymerisation and binds preferentially to mitotic microtubules, only affecting axonal microtubules at high concentrations. The induction of tubulin spiralisation 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

Pharmacokinetic parameters of vinorelbine were evaluated in blood.

#### Distribution

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

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

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

#### Biotransformation

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

#### Elimination

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

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

#### Special patient groups

##### Renal impairment

The effects of renal dysfunction on vinorelbine disposition have not been assessed.

However, dose reduction in case of reduced renal function is not indicated due to the low renal elimination.



### Liver impairment

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

A phase I pharmacokinetic dose-adjusted study was conducted in cancer patients with liver dysfunction: 6 patients with moderate dysfunction (Bilirubin  $< 2 \times$  UNL and Transaminases  $< 5 \times$  UNL) treated up to 25 mg/m<sup>2</sup> and 8 patients with severe dysfunction (Bilirubin  $> 2 \times$  UNL and/or Transaminases  $> 5 \times$  UNL) treated up to 20 mg/m<sup>2</sup>. Mean total clearance in these two subsets of patients was similar to that in patients with normal hepatic function. Therefore, the pharmacokinetics of vinorelbine are not modified in patients presenting with moderate or severe liver impairment. 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 is required (see sections 4.2 and 4.4).

### Elderly patients

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

### PK-PD relation

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

## **5.3 Preclinical safety data**

### Mutagenic and carcinogenic potential

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 cardiovascular system.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Water for injections

Sodium hydroxide (for pH-adjustment)

### **6.2 Incompatibilities**

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

Vinorelbine Martindale Pharma must not be mixed with other medicinal products except those mentioned in section 6.6.

### **6.3 Shelf Life**

As packaged for sale: 2 Years.

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

#### **6.4 Special precautions for storage**

As packaged for sale: Store in a refrigerator (2°C – 8°C). Do not freeze. Keep the vial in the outer carton in order to protect from light.

For storage condition of the diluted medicinal product, see section 6.3.

#### **6.5 Nature and contents of container**

Clear type I glass vial with Teflon coated rubber butyl stopper, the stopper is covered with a crimped-on aluminium cap equipped with a flip-off polypropylene seal.

Pack sizes: 1 ml and 5 ml. Available as single packs.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal**

Only trained staff should carry out the preparation and administration of Vinorelbine Martindale Pharma<sup>®</sup>. Suitable safety, equipment, disposable gloves, facemask and disposable apron should be worn.

Spills and leakages must be wiped up.

All contact with the eye must be strictly avoided. Immediate washing of the eye with normal saline solution should be undertaken if any contact occurs.

On completion of preparation and administration, any exposed surfaces should be thoroughly cleaned and hands and face washed.

There is no incompatibility between Vinorelbine Martindale Pharma and clear glass vials, PVC or vinyl acetate bags, or infusion sets with PVC tubing.

Vinorelbine may be administered by slow bolus (5-10 minutes) after dilution in 20 – 50 ml 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.

Vinorelbine should only be given intravenously. 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.

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

## **7 MARKETING AUTHORISATION HOLDER**

Cardinal Health UK 434 Limited (T/A Cardinal Health)  
Bampton Road  
Harold Hill  
Romford, Essex  
RM3 8UG  
United Kingdom

## **8 MARKETING AUTHORISATION NUMBER**

PA1348/16/1

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 25th September 2009

## **10 DATE OF REVISION OF THE TEXT**