IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA1380/061/001
Case No: 2055656

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

Actavis Group PTC ehf

Reykjavikurvegi 76-78, **220 Hafnarfjordur**, **Iceland**

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

Vinorelbine 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 **12/12/2008** until **11/12/2013**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vinorelbine 10 mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each 1 ml vial contains 10 mg vinorelbine (as tartrate).
Each 5 ml vial contains 50 mg vinorelbine (as tartrate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, colourless to slightly yellow solution with a pH of 3.3 to 3.8 and an osmolarity of about 330mOsm/l.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Vinorelbine is indicated in the treatment of:

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

4.2 Posology and method of administration

'For intravenous infusion only'

Vinorelbine 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 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.

Non-small cell lung cancer
As a single agent the normal dose is 25-30mg/m², administered once weekly. In polychemotherapy the schedule regimen is a function of the protocol. The normal dose could be used (25-30mg/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 25-30mg/m², administered once weekly.

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

For Adults Only: Safety and efficacy in children have not been determined.

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).

4.3 Contraindications

- The use of intrathecal route is contra-indicated
- 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.

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 should not be given concomitantly with radiotherapy if the treatment field 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).
- This product is generally not recommended in combination with live attenuated vaccines, phenytoin and itraconazol.
- 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 vinorelbin 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 vinorelbin 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

The undesirable effects that have been reported in more than isolated cases are listed below after organ system and frequency. The frequency is defined using the following convention:
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), not known (cannot be estimated from the available data).

Infections and infestations
Common: Infection.

Blood and lymphatic system disorders
Very common: Neutropenia, anaemia.
Common: Thrombocytopenia, febrile neutropenia, neutropenic sepsis with potential fatal outcome.

Immune system disorders
Common: Allergic reactions (skin reactions, respiratory reactions).

Metabolism and nutrition disorders
Rare: Severe hyponatraemia.
Very rare: Inappropriate antidiuretic hormone secretion (SIADH).

Nervous system disorders
Very common: Constipation (see also “Gastrointestinal disorders”), loss of deep tendon reflexes.
Common: Paraesthesia with sensory and motor symptoms.
Rare: Weakness of lower extremities, paralytic ileus (see also “Gastrointestinal disorders”).
Very rare: Guillain-Barré syndrome.

Cardiac disorders
Rare: Ischaemic heart disease like angina pectoris, electrocardiogram changes, myocardial infarction.

Respiratory, thoracic and mediastinal disorders
Common: Dyspnoea, bronchospasm.
Rare: Interstitial lung disease.

Gastrointestinal disorders
Very common: Constipation (see also “Nervous system disorders”), nausea, vomiting, diarrhoea, stomatitis, oesophagitis, anorexia.
Rare: Pancreatitis, paralytic ileus (see also “Nervous system disorders).

Hepatobiliary disorders
Very common: Abnormal liver function values (total bilirubin increased, alkaline phosphatase increased, aspartate aminotransferase increased, alanine aminotransferase increased).

Skin and subcutaneous tissue disorders
Very common: Alopecia.
Common: Skin reactions.

Musculoskeletal and connective tissue disorders
Common: Myalgia, arthralgia.
Rare: Jaw pain.

Renal and urinary disorders
Common: Creatinine increased.

General disorders and administration site conditions
Very common: Fatigue, fever, pain in different locations, asthenia, injection site erythema, injection site pain, injection site discolouration, injection site phlebitis.
Rare: Injection site necrosis.

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
Bone marrow depression that mainly results in neutropenia (G3 : 24.3%; G4 : 27.8%), reversible within 5 to 7 days and non-cumulative over time.
Febrile neutropenia and neutropenic sepsis which in some cases (1.2%) had a fatal outcome. Anaemia (G3-4: 7,4%), thrombocytopenia (G3-4: 2.5%) may occur, but is seldom severe.

Immune system disorders
Allergic reactions (skin reactions, respiratory reactions).
Metabolism and nutrition disorders: Severe hyponatraemia and inappropriate antidiuretic hormone secretion (SIADH) have been reported.

Nervous system disorders
Neurological adverse reactions (G3: 2.6%; G4: 0.1% including loss of deep tendon reflexes. Very rarely Guillain-Barré syndrome.
Weakness of the lower limbs has been reported after treatment with long duration.
Paraesthesiae with sensory and motor symptoms (G3-4: < 3%). These symptoms are normally reversible when the treatment is discontinued.
Effects on the autonomic nervous system causing intestinal paresis and constipation. Seldom this progresses to paralytic ileus (< 3%). See also “Gastrointestinal disorders“.

Cardiac disorders
Ischaemic heart disease (angina pectoris and/or transitory electrocardiogram changes, myocardial infarction).

Respiratory, thoracic and mediastinal disorders
Dyspnoea and bronchospasm may occur during treatment of vinorelbine, as with other vinca alkaloids. There have been rare reports of interstitial pneumopathy, especially in patients who are treated with a combination of vinorelbine and mitomycin.

Gastrointestinal disorders
Stomatitis (G1: 7.6%, G2: 3.6%, G3: 0.7%, G4: 0.1% with vinorelbine as single agent) and oesophagitis. Nausea and vomiting (G1: 19.9%, G2: 8.3%, G3: 1.9%, G4: 0.3%) Anti-emetic therapy reduces these undesirable effects.
Constipation is the main symptom (G3-4: 2.7%) this rarely develops into paralytic ileus with vinorelbine as single agent and in combination with other chemotherapy (G3-4: 4.1%). Diarrhoea, normally mild to moderate, may occur.
Paralytic ileus, treatment can be re-uptaken when normal gastrointestinal function is established. Pancreatitis has been reported. Anorexia (G1-2:14%, G3:1%)

Hepatobiliary disorders
Transient elevations of liver function tests (G1-2) without clinical symptoms have been reported (Bilirubin, alkaline phosphatase, ASAT in 27.6% and ALAT in 29.3%).

Skin and subcutaneous tissue disorders
Alopecia, normally mild, can occur (G3-4: 4.1% with vinorelbine as a single agent). General skin reactions such as rash, pruritis, urticaria and erythema of the hands and feet have been reported with vinorelbine.

Musculoskeletal and connective tissue disorders
Arthralgia including jaw pain and myalgia.

Renal and urinary disorders
Increased blood creatinine has been reported.

General disorders and administration site conditions
As with other Vinca alkaloids Vinorelbine has a moderate vesicant power. Fatigue, fever, asthenia, pain at different sites including chest pain and pain at the site of the tumour have been experienced by patients that have been treated with vinorelbine. Reactions at the site of injection may include erythema, burning pain, discolouration of the vein and local phlebitis (G3: 3.6%; G4: 0.1% with vinorelbine as a single agent). Local necrosis has been observed. Correct placement of the intravenous cannula or catheter and liberal flushing of the vein can limit these effects.

4.9 Overdose

Overdosages may produce 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 known 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 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 a cytostatic drug of the Vinca alkaloid family.

Vinorelbine 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, the blood concentration-time profile, is characterised by a three exponential elimination curve. The terminal half-life was on average around 40 hours. Clearance in blood is high, close to the hepatic blood flow and was on average 0,72 l/h/kg (interval: 0,32-1,26 l/h/kg), while the volume of distribution at steady-state was large, on average 21,2 l/kg, showing signs of extensive tissue distribution. There is weak binding to plasma proteins (13.5%), but strong binding to blood cells, especially to platelets (78%). 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 and the main metabolite is 4-O-deacetylvinorelbine.

Renal excretion is low (< 20% of the dose) and consists mainly of the parent compound. Excretion via the biliary route is the most important route of elimination, both for metabolites and unchanged vinorelbine.
The effects of reduced kidney function on the vinorelbine disposition have not been evaluated, but a dose reduction is not necessary due to the low 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 is required (see sections 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

Water for injections.

6.2 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.

6.3 Shelf Life

As packaged for sale
3 years.

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

Shelf-life after dilution
The physicochemical and microbiological stability of the drug product after dilution in the recommended solutions for infusion (see section 6.6) has been demonstrated for 24 hours at 2-8°C 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.

6.4 Special precautions for storage

As packaged for sale
Store in a refrigerator (2°C - 8°C). Keep the vial in the outer carton in order to protect from light.
Do not freeze.
For storage condition of the diluted medicinal product, see section 6.3

6.5 Nature and contents of container

1ml vial: Colourless glass vial (type I) with bromobutyl rubber stopper and metallic cap with red coloured polypropylene disk.
5ml vial: Colourless glass vial (type I) with bromobutyl rubber stopper and metallic cap with green coloured polypropylene disk.

Pack-sizes:
1 x 1 ml vial
10 x 1 ml vial
1 x 5 ml vial
10 x 5 ml vial

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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 long 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 an ophthalmologist should be contacted.
In case of skin contact, the affected area should be thoroughly washed with water.

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

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

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.

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.

Excreta and vomit must be handled with care.

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 1380/61/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd August 2008

10 DATE OF REVISION OF THE TEXT

December 2008