ART026093P
VINORELBINE TARTRATE MY 20MG 30MG 80MG X1 CAPS PIL

lotus PHARMACEUTICAL

GENERAL INFORMATION

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REGULATORY APPROVAL

Package Insert

VINOBIN SOFT CAPSULES 20 mg
VINOBIN SOFT CAPSULES 30 mg
VINOBIN SOFT CAPSULES 80 mg

Vinorelbine

Glue Point

VINOBIN SOFT CAPSULES 20 mg
VINOBIN SOFT CAPSULES 30 mg
VINOBIN SOFT CAPSULES 80 mg
Vinorelbine

15mm

15mm

Glue Point

1. NAME OF THE MEDICINAL PRODUCT

VINOBIN SOFT CAPSULES 20 mg
VINOBIN SOFT CAPSULES 30 mg
VINOBIN SOFT CAPSULES 80 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VINOBIN SOFT CAPSULES 20 mg: Each soft capsule contains 20mg vinorelbine (as tartrate)
VINOBIN SOFT CAPSULES 30 mg: Each soft capsule contains 30mg vinorelbine (as tartrate)
VINOBIN SOFT CAPSULES 80 mg: Each soft capsule contains 80mg vinorelbine (as tartrate)

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Soft capsule.
VINOBIN SOFT CAPSULES 20mg - An oval-shaped light brown soft capsule filled with a transparent, colorless to slightly yellow liquid.
VINOBIN SOFT CAPSULES 30mg - An oblong-shaped pink soft capsule filled with a transparent, colorless to slightly yellow liquid
VINOBIN SOFT CAPSULES 80mg - An oblong-shaped pale yellow soft capsule filled with a transparent, colorless to slightly yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
For treatment of Non-small cell lung cancer / Advanced Breast Cancer

4.2 Posology and method of administration
Vinorelbine soft capsules must be given strictly by the oral route. Vinorelbine soft capsules should be swallowed with water without chewing or sucking the capsule. It is recommended to take the capsule with some food.

As a single agent:
The recommended regimen is:
First three administrations
60mg/m² of body surface area, administered once weekly

Subsequent administrations
Beyond the third administration, it is recommended to increase the dose of Vinorelbine soft capsules to 80mg/m² once weekly except in those patients for whom the neutrophil count dropped once below 500/mm³ or more than once between 500 and 1 000/mm³ during the first three administrations at 60mg/m².

Neutrophil count during the first 3 administrations of 60mg/m²/week	Neutrophils > 1000	Neutrophils ≥ 500 and < 1000 (1 episode)	Neutrophils ≥ 500 and < 1000 (2 episodes)	Neutrophils < 500
Recommended dose Starting with the 4th administration	80		60	

Dose modification
For any administration planned to be given at 80mg/m², if the neutrophil count is below 500/mm³, the administration should be delayed until recovery and the dose reduced from 80 to 60mg/m² per week during the 3 following administrations.

Neutrophil count beyond the 4th administrations of 60mg/m²/week	Neutrophils > 1000	Neutrophils ≥ 500 and < 1000 (1 episode)	Neutrophils ≥ 500 and < 1000 (2 episodes)	Neutrophils < 500
Recommended dose starting for the next administration	80		60	

It is possible to reescalate the dose from 60 to 80 mg/m² per week if the neutrophil count did not drop below 500/mm³ or more than once between 500 and 1 000/mm³ during 3 administrations given at 60 mg/m² according to the rules previously defined for the first 3 administrations.

For combination regimens, the dose and schedule will be adapted to the treatment protocol
Based on clinical studies, the oral dose of 80 mg/m² was demonstrated to correspond to 30 mg/m² of the IV form and 60 mg/m² to 25 mg/m².

This has been the base for combination regimens alternating IV and oral forms improving patient's convenience.

For combination regimens, the dose and schedule will be adapted to the treatment protocol.

Even for patients with BSA ≥ 2 m² the total dose should never exceed 120 mg per week at 60 mg/m² and 160 mg per week at 80 mg/m².

Administration in the elderly
Clinical experience has not detected any significant differences among elderly patients with regards to response rate, although greater sensitivity in some of these patients cannot be excluded. Age does not modify the pharmacokinetics of Vinorelbine Soft Capsule.

Administration in children
Safety and efficacy in children have not been established and administration is therefore not recommended (see section 5.1).

Administration in patients with liver insufficiency
Vinorelbine Soft Capsule can be administered at the standard dose of 60 mg/m²/week in patients with mild liver impairment (bilirubin < 1.5 x ULN, and ALAT and/or ASAT from 1.5 to 2.5 x ULN). In patients with moderate liver impairment (bilirubin from 1.5 to 3 x ULN, whatever the levels of ALAT and ASAT), Vinorelbine Soft Capsule should be administered at a dose of 50 mg/m²/week. The administration of Vinorelbine Soft Capsule in patients with severe hepatic impairment is not recommended as there is insufficient data to determine the pharmacokinetics, efficacy, and safety of Vinorelbine Soft Capsule in this population (see sections 4.4, and 5.2)

Administration in patients with renal insufficiency
Given the minor renal excretion, there is no pharmacokinetic justification for reducing the dose of Vinorelbine Soft Capsule in patients with serious renal insufficiency (see sections 4.4, 5.2).
Section Instructions for use and handling of oral Vinorelbine Soft Capsule (see section 6.6)

4.3 Contraindications
- Known hypersensitivity to vinorelbine or other vinca-alkaloids or to any of the constituents.
- Disease significantly affecting absorption
- Previous significant surgical resection of stomach or small bowel.
- Neutrophil count < 1500/mm³ or severe infection current or recent (within 2 weeks).
- Platelet count < 100000/mm³
- Severe hepatic insufficiency
- Pregnancy: see section 4.6
- Lactation: see section 4.6
- Patients requiring long-term oxygen therapy
- In combination with yellow fever vaccine: see section 4.5

4.4 Special warnings and precautions for use
Special warnings
Vinobin should be prescribed by a physician who is experienced in the use of chemotherapy with facilities for monitoring cytotoxic drugs.

If the patient chews or sucks the capsule by error, the liquid is an irritant. Proceed to mouth rinses with water or preferably a normal saline solution.

In the event of the capsule being cut or damaged, the liquid content is an irritant, and so may cause damage if in contact with skin, mucosa or eyes. Damaged capsules should not be swallowed and should be returned to the pharmacy or to the doctor in order to be properly destroyed. If any contact occurs, immediate thorough washing with water or preferably with normal saline solution should be undertaken.

In the case of vomiting within a few hours after drug intake, do not re-administer. Supportive treatment such as metoclopramide or 5HT3 antagonists (e.g. ondansetron, granisetron) may reduce the occurrence of this: see section 4.5. Vinobin soft capsule is associated with a higher incidence of nausea/vomiting than the intravenous formulation. Primary prophylaxis with antiemetics and administration of the capsules with some food is recommended as this has also been shown to reduce the incidence of nausea and vomiting: see section 4.2.

Patients receiving concomitant morphine or opioid analgesics: laxatives and careful monitoring of bowel mobility are recommended. Prescription of laxatives may be appropriate in patients with prior history of constipation.

Close haematological monitoring must be undertaken during treatment (determination of haemoglobin level and the leucocyte, neutrophil and platelet counts on the day of each new administration).

Dosing should be determined by haematological status:
- If the neutrophil count is below 1500 /mm³ and/or the platelet count is below 100000/mm³, then the treatment should be delayed until recovery.
- For dose escalation from 60 to 80 mg/m² per week, after the third administration: see section 4.2.
- For the administrations given at 80mg/m², if the neutrophil count is below 500/mm³ or more than once between 500 and 1000 /mm³, then the treatment should be delayed until recovery. The administration should not only be delayed but also reduced to 60mg/m² per week. It is possible to reescalate the dose from 60 to 80 mg/m2 per week: see section 4.2.

Where treatments were initiated at 80 mg/m2, a few patients developed excessive neutropenic complications including those with a poor performance status. Therefore, it is recommended that the starting dose should be 60 mg/m2 escalating to 80 mg/m2 if the dose is tolerated as described in section 4.2.

If patients present signs or symptoms suggestive of infection, a prompt investigation should be carried out.

The additive effect of concomitantly administered product containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

The small amount of alcohol in this medicinal product will not have any noticeable effects.
Special precautions for use
Special care should be taken when prescribing for patients with:
- history of ischemic heart disease: see section 4.8
- poor performance status

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

Oral Vinobin was studied in patients with liver impairment at the following doses:
- 60 mg/m² in patients with mild liver impairment (bilirubin < 1.5 x ULN, and ALAT and/or ASAT from 1.5 to 2.5 x ULN);
- 50 mg/m² in patients with moderate liver impairment (bilirubin from 1.5 to 3 x ULN, whatever the levels of ALAT and ASAT).

Safety and pharmacokinetics of vinorelbine were not modified in these patients at the tested doses.
Oral Vinobin was not studied in patients with severe hepatic impairment, therefore its use is not recommended in these patients

As there is a low level of renal excretion there is no pharmacokinetic rationale for reducing the dose of Vinobin in patients with impaired kidney function

Route of Administration
Oral

4.5 Interaction with other medicinal products and other forms of interaction
Concomitant use contraindicated
Yellow fever vaccine: as with all cytotoxics, risk of fatal generalised vaccine disease: see section 4.3.

Concomitant use not recommended
Live attenuated vaccines: (for yellow fever vaccine, see concomitant use contraindicated) as with all cytotoxics, risk of generalised vaccine disease, possibly fatal. This risk is increased in patients already immunodepressed by their underlying disease. It is recommended to use an inactivated vaccine when one exists (e.g. poliomyelitis): see section 4.4
Phenytoin: as with all cytotoxics, risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic drug or risk of toxicity enhancement or loss of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin.
Itraconazole: as with all vinca-alkaloids, increased neurotoxicity of vinca-alkaloids due to the decrease of their hepatic metabolism.

Concomitant use to take into consideration
Cisplatin: There is no mutual pharmacokinetic interaction when combining Vinorelbine Soft Capsule with cisplatin over several cycles of treatment. However, the incidence of granulocytopenia associated with Vinorelbine Soft Capsule use in combination with cisplatin is higher than associated with Vinorelbine Soft Capsule single agent.
Mitomycin C: risk of bronchospasm and dyspnoea are increased, in rare case an interstitial pneumonitis was observed.
Ciclosporin, tacrolimus: excessive immunodepression with risk of lymphoproliferation.
As vinca-alkaloids are known as substrates for P-glycoprotein, and in the absence of specific study, caution should be exercised when combining Vinorelbine Soft Capsule with strong modulators of this membrane transporter.
The combination of VINORELBINE SOFT CAPSULE with other drugs with known bone marrow toxicity is likely to exacerbate the myelosuppressive adverse effects.
No clinically significant pharmacokinetic interaction was observed when combining Vinorelbine Soft Capsule with several other chemotherapeutic agents (paclitaxel, docetaxel, capecitabine and oral cyclophosphamide).
As CYP3A4 is mainly involved in the metabolism of vinorelbine, combination with strong inhibitors of this isoenzyme (e.g. azole antifungals such as ketoconazole and itraconazole) could increase blood concentrations of vinorelbine and combination with strong inducers of this isoenzyme (e.g. rifampicin, phenytoin) could decrease blood concentrations of vinorelbine.
Anti-emetic drugs such as $5HT_3$ antagonists (e.g. ondansetron, granisetron) do not modify the pharmacokinetics of Vinorelbine Soft Capsule soft capsules (see section 4.4).
Anticoagulant treatment: as with all cytotoxics, the frequency of INR (International Normalised Ratio) monitoring should be increased due to the potential interaction with oral anticoagulants and increased variability of coagulation in patients with cancer.
Food does not modify the pharmacokinetics of vinorelbine.

4.6 Fertility, pregnancy and lactation
Pregnancy
Vinorelbine Soft Capsule is suspected to cause serious birth effects when administered during pregnancy: see section 5.3.
Vinorelbine Soft Capsule is contra-indicated in pregnancy: see section 4.3.
In case of a vital indication for treatment with Vinorelbine Soft Capsule during pregnancy a medical consultation concerning the risk of harmful effects for the child should be conducted.
If pregnancy occurs during treatment genetic counseling should be offered.

Women of child-bearing potential
Women of child-bearing potential must use effective contraception during treatment and up to 3 months after treatment: see section 4.3

Lactation
It is unknown whether vinorelbine is excreted in human breast milk.
The excretion of vinorelbine in milk has not been studied in animal studies.
A risk to the suckling child cannot be excluded therefore breast feeding must be discontinued before starting treatment with Vinorelbine Soft Capsule: see section 4.3.

Fertility
Men being treated with Vinorelbine Soft Capsule are advised not to father a child during and minimally up to 3 months after treatment: see section 4.3.
Prior to treatment advice should be sought for conserving sperm due to the chance of irreversible infertility as a consequence of treatment with vinorelbine.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed but on the basis of the pharmacodynamic profile vinorelbine does not affect the ability to drive and use machines. However, caution is necessary in patients treated with vinorelbine considering some adverse effects of the drug: see section 4.8.

4.8 Undesirable effects
Adverse reactions reported are listed below, by system organ and by frequency: Very common, common, uncommon, rare, very rare & not known.

Undesirable effects reported with Vinorelbine Soft Capsule soft capsule:

Pre-marketing experience:

The most commonly reported adverse drug reactions are bone marrow depression with neutropenia, anaemia and thrombocytopenia, gastrointestinal toxicity with nausea, vomiting, diarrhoea, stomatitis and constipation. Fatigue and fever were also reported very commonly.

Post-marketing experience:

Vinorelbine Soft Capsule soft capsule is used as single agent or in combination with other chemotherapeutic agents or targeted therapy agents such as cisplatin or capecitabine. The most commonly system organ classes involved during post-marketing experience are: 'Blood and lymphatic system disorders', 'Gastrointestinal disorders', 'Infections and infestations' and 'General disorders and administration site conditions'. This information is consistent with the pre-marketing experience.

Infections and infestations	
Very common:	Bacterial, viral or fungal infections without neutropenia at different sites
Common:	Bacterial, viral or fungal infections resulting from bone marrow depression and/or immune system compromise (neutropenic infections) are usually reversible with an appropriate treatment. Neutropenic infection
Not known:	Neutropenic sepsis. Complicated septicaemia and sometimes fatal Severe sepsis sometimes with other organ failure Septicaemia
Blood and lymphatic disorders	
Very common:	Bone marrow depression resulting mainly in neutropenia is reversible and is the dose limiting toxicity Leucopenia Anaemia Thrombocytopenia.
Common:	Neutropenia associated with fever over 38ºC including febrile neutropenia.
Not known:	Thrombocytopenia Pancytopenia
Endocrine disorders	
Not known:	Inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	
Very common:	Anorexia
Not known:	Severe hyponatraemia.
Psychiatric disorders	
Common:	Insomnia
Nervous system disorders	
Very common:	Neurosensory disorders generally limited to loss of tendon reflexes and infrequently severe.
Common:	Neuromotor disorders Headache Dizziness Taste disorders
Uncommon:	Ataxia grade 3
Eye disorders	
Common:	Visual impairment
Cardiac disorders	
Uncommon:	Heart failure and cardiac dysrhythmia
Not known:	Myocardial infarction in patients with cardiac medical history or cardiac risk factors.
Vascular disorders	
Common:	Arterial hypertension Arterial hypotension
Respiratory system, thoracic and mediastinal disorders	
Common:	Dyspnoea Cough
Gastrointestinal disorders	
Very Common:	Nausea Vomiting supportive treatment (such as oral setrons) may reduce the occurrence of nausea and vomiting: Diarrhoea Stomatitis Abdominal pain: Constipation. Prescription of laxatives may be appropriate in patients with prior history of constipation and/or who receive concomitant treatment with morphine or morphine-mimetics Gastric disorders
Common:	Oesophagitis Dysphagia
Uncommon:	Paralytic ileus [exceptionally fatal], treatment may be resumed after recovery of normal bowel mobility.
Not known:	Gastro-intestinal bleeding.
Hepatobiliary disorders	
Common:	Hepatic disorders
Not known :	Transient elevations of liver function tests
Skin and subcutaneous tissue disorders	
Very common:	Alopecia usually mild in nature may occur.
Common:	Skin reactions:
Musculoskeletal and connective tissue disorders	
Common:	Arthralgia including jaw pain, Myalgia
Renal and urinary disorders	
Common:	Dysuria Other genitourinary symptom
General disorders and administration site conditions	
Very common:	Fatigue/malaise Fever
Common:	Pain including pain at the tumour site Chills
Investigations	
Very common:	Weight loss
Common:	Weight gain

4.9 Overdose

Symptoms

Overdosage with Vinorelbine Soft Capsule soft capsules could produce bone marrow hypoplasia sometimes associated with infection, fever, paralytic ileus and hepatic disorders.

Emergency procedure

General supportive measures together with blood transfusion, growth factors, and broad spectrum antibiotic therapy should be instituted as deemed necessary by the physician. A close monitoring of hepatic function recommended.

Antidote

There is no known antidote for overdosage of Vinorelbine Soft Capsule.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vinca alkaloids and analogues (ATC Code: L01C A04)
Vinorelbine Soft Capsule is a antineoplastic drug of the vinca alkaloid family but unlike all the other vinca alkaloids, the catharantine moiety of vinorelbine has been structurally modified. At the molecular level, it acts on the dynamic equilibrium of tubulin in the microtubular apparatus of the cell. It inhibits tubulin polymerization and binds preferentially to mitotic microtubules, affecting axonal microtubules at high concentrations only. The induction of tubulin spiralization is less than that produced by vincristine.
Vinorelbine Soft Capsule blocks mitosis at G2-M, causing cell death in interphase or at the following mitosis.
Safety and efficacy of Vinorelbine Soft Capsule in paediatric patients have not been established.

5.2 Pharmacokinetic properties

Pharmacokinetic parameters of Vinorelbine were evaluated in blood

Absorption

After oral administration, vinorelbine is rapidly absorbed and the T_{max} is reached between 1.5 to 3 h with a blood concentration peak (C_{max}) of approximately 130 ng/ml after a dose of 80 mg/m^2.
Absolute bioavailability is approximately 40% and a simultaneous intake of food does not alter the exposure to vinorelbine.
Oral vinorelbine at 60 and 80 mg/m^2 leads to blood exposure comparable to that achieved with intravenous vinorelbine at 25 and 30 mg/m^2, respectively.
The blood exposure to vinorelbine increases proportionally with the dose up to 100mg/m^2.
Interindividual variability of the exposure is similar after administration by intravenous and oral routes.

Distribution

The steady-state volume of distribution is large, on average 21.2 l.kg^{-1}(range: 7.5 - 39.7 l.kg^{-1}), which indicates extensive tissue distribution.
Binding to plasma proteins is weak (13.5%), vinorelbine binds strongly to blood cells and especially to platelets (78%).
There is a significant uptake of vinorelbine in lungs, as assessed by pulmonary surgical biopsies which showed concentration up to a 300- fold higher concentration than in serum.
Vinorelbine is not found in the central nervous system.

Biotransformation

All metabolites of vinorelbine are formed by CYP3A4 isoform of cytochromes P450, except 4-O-deacetylvinorelbine likely to be formed by carboxylesterases. 4-O-deacetylvinorelbine is the only active metabolite and the main one observed in blood.
Neither sulfate nor glucuronide conjugates are found.

Elimination

The mean terminal half-life of vinorelbine is around 40 hours. Blood clearance is high, approaching hepatic blood flow, and is 0.72 l.h^{-1}.kg^{-1} (range: 0.32-1.26 l.h^{-1}.kg^{-1}).
Renal elimination is low (<5 % of the dose administered) and consists mostly in parent compound. Biliary excretion is the predominant elimination route of both unchanged vinorelbine, which is the main recovered compound, and its metabolites.

Special patients groups

Renal and liver impairment:

There is no data on effects of renal dysfunction on the pharmacokinetics of vinorelbine. However, dose reduction in case of reduced renal function is not indicated with vinorelbine due to the low level of renal elimination.
Total clearance of vinorelbine was neither modified between mild and moderate impairment nor was it altered in hepatically impaired patients when compared with clearance in patients with normal liver function.
No data is available for patients with severe liver impairment therefore Vinorelbine Soft Capsule is contra-indicated in these patients: see sections 4.2, 4.3 and 4.4.

Elderly patients

It is demonstrated that pharmacokinetics of vinorelbine were not influenced by age. However, since elderly patients are frail, caution should be exercised when increasing the dose of Vinorelbine Soft Capsule soft capsule: see section 4.2.

Pharmacokinetics/Pharmacodynamic relationships

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Fill solution:
Purified water
Polysorbate 80
Macrogol 400
Ethanol 96%
Medium Triglycerides chain

Vinorelbine 20 mg & 80mg soft capsule
Shell capsule:
Gelatin
Sorbitol Liquid
Yellow Iron oxide
Titanium dioxide
Purified Water

Vinorelbine 30 mg soft capsule
Shell capsule:
Gelatin
Sorbitol Liquid
Red Iron oxide
Titanium dioxide
Purified Water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Please refer to the outer carton.

6.4 Special precautions for storage

This medicinal product needs to be stored at 2-8ºC (in a refrigerator). Store in original container. Keep the immediate packaging tightly closed

6.5 Nature and contents of container

PVC/PVDC-Al blister with child-resistant safety paper layer of 1's capsule packed into an outer carton with a pack insert

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.
Instructions for use/handling
To open the packaging:
1. Cut the blister along the black dotted line
2. Peel the soft plastic foil off
3. Push the capsule through the aluminium foil.

7. PRODUCT REGISTRATION HOLDER

Lotus Healthcare Malaysia Sdn. Bhd.
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8. MANUFACTURER

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9. DATE OF REVISION OF THE TEXT

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