NAME OF THE MEDICINAL PRODUCT

Vinorelbine Alvogen 20 mg soft capsule
Vinorelbine Alvogen 30 mg soft capsule
Vinorelbine Alvogen 80 mg soft capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains vinorelbine tartrate 27.70 mg equivalent to 20 mg vinorelbine.
Each soft capsule contains vinorelbine tartrate 41.55 mg equivalent to 30 mg vinorelbine.
Each soft capsule contains vinorelbine tartrate 110.80 mg equivalent to 80 mg vinorelbine.

Excipient with known effect
Each soft capsule containing 20 mg vinorelbine contains 38.439 mg sorbitol.
Each soft capsule containing 30 mg vinorelbine contains 59.850 mg sorbitol.
Each soft capsule containing 80 mg vinorelbine contains 99.905 mg sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsule

Vinorelbine Alvogen 20 mg soft capsule: An oval-shaped light brown soft capsule, with the size of 11x7 mm filled with a transparent, colourless to slightly yellow liquid.
Vinorelbine Alvogen 30 mg soft capsule: An oblong-shaped pink soft capsule, with the size of 18x6 mm filled with a transparent, colourless to slightly yellow liquid.
Vinorelbine Alvogen 80 mg soft capsule: An oblong-shaped pale yellow soft capsule, with the size of 21x8 mm filled with a transparent, colourless to slightly yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vinorelbine is indicated in adults for:
- Non-small cell lung cancer
- Advanced Breast Cancer.

4.2 Posology and method of administration

Posology
- **As a single agent:**

Adult patients
The recommended regimen is:

First three administrations
60 mg/m² of body surface area, administered once weekly

Subsequent administrations
After the third administration, it is recommended to increase the dose of vinorelbine to 80 mg/m² once weekly except in those patients for whom the neutrophil count dropped once <500/mm^3 or more than once between 500 and 1,000/mm^3 during the first three administrations at 60 mg/m².

Neutrophil count during the first 3 administrations of 60 mg/m^2/week	Neutrophils >1,000	Neutrophils >500 and <1,000 (1 episode)	Neutrophils >500 and <1,000 (2 episodes)	Neutrophils <500
Recommended dose starting with the 4th administration	80	80	60	60

- **Dose modification**

For any administration planned to be given at 80 mg/m², if the neutrophil count is below 500/mm^3, the administration should be delayed until recovery and the dose reduced from 80 to 60 mg/m^2 per week during the 3 following administrations.

Neutrophil count beyond the 4th administration of 80 mg/m^2/week	Neutrophils >1,000	Neutrophils >500 and <1,000 (1 episode)	Neutrophils >500 and <1,000 (2 episodes)	Neutrophils <500
Recommended dose starting with the next administration	80		60	

It is possible to re-escalate the dose from 60 to 80 mg/m^2 per week if the neutrophil count did not drop below 500/mm^3 or more than once between 500 and 1,000/mm^3 during 3 administrations given at 60 mg/m^2 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/m^2 was demonstrated to correspond to 30 mg/m^2 of the IV form and 60 mg/m^2 to 25 mg/m^2.
This has been the base for combination regimens alternating IV and oral forms improving patient convenience.

For combination regimens, the dose and schedule will be adapted to the treatment protocol. The following table gives the dose required for appropriate ranges of body surface area (BSA).

	60 mg/m^2	80 mg/m^2
BSA (m^2)	Dose (mg)	Dose (mg)
0.95 to 1.04	60	80
1.05 to 1.14	70	90
1.15 to 1.24	70	100
1.25 to 1.34	80	100
1.35 to 1.44	80	110
1.45 to 1.54	90	120
1.55 to 1.64	100	130
1.65 to 1.74	100	140
1.75 to 1.84	110	140
1.85 to 1.94	110	150
≥ 1.95	120	160

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

Elderly
Clinical experience has not detected any significant differences among elderly patients with regard to the response rate, although greater sensitivity in some of these patients cannot be excluded. Age does not modify the pharmacokinetics of vinorelbine (see section 5.2).

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

Hepatic insufficiency
Vinorelbine 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 should be administered at a dose of 50 mg/m²/week. The administration of vinorelbine in patients with severe hepatic impairment is not recommended as there is insufficient data to determine the pharmacokinetics, efficacy and safety of vinorelbine in this population (see sections 4.3, 4.4, 5.2).

Renal insufficiency
Given the minor renal excretion, there is no pharmacokinetic justification for reducing the dose of vinorelbine in patients with serious renal insufficiency (see sections 4.4 and 5.2).

Method of administration

Vinorelbine must be given strictly by the oral route.
Vinorelbine must be swallowed whole with water, without chewing, sucking or dissolving the capsule.
It is recommended to administer the capsule with some food.

4.3 Contraindications

- Hypersensitivity to the active substance, other vinca-alkaloids or to any of the excipients listed in section 6.1
- Disease significantly affecting absorption
- Previous significant surgical resection of stomach or small bowel.
- Neutrophil count <1,500/mm^3 or severe infection current or recent (within 2 weeks).
- Platelet count <100,000/mm^3
- 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
Vinorelbine 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 rinse mouth 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, hospital 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, never repeat the administration of this dose. Supportive treatment such as 5HT3 antagonists setron (e.g. ondansetron, granisetron) may reduce the occurrence of this (see section 4.5)..

Vinorelbine 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. Due to

sorbitol content, patient with rare hereditary problems with fructose intolerance should not take the capsules.

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 1,500/mm^3 and/or the platelet count is below 100,000/mm^3, then the treatment should be delayed until recovery. (see section 4.2).
- For dose escalation from 60 to 80 mg/m^2 per week, after the third administration: see section 4.2.
- For the administrations given at 80 mg/m², if the neutrophil count is below 500/mm^3 or more than once between 500 and 1,000/mm^3, the administration should not only be delayed but also reduced to 60mg/m^2 per week. It is possible to reescalate the dose from 60 to 80 mg/m^2 per week (see section 4.2).

During clinical trials where treatments were initiated at 80 mg/m^2, 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/m^2 escalating to 80mg/m^2 if the dose is tolerated (see section 4.2).

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

Special precautions for use
Special care should be taken when prescribing for patients with:
- history of ischemic heart disease
- poor performance status.

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

Use of this medicine with live attenuated vaccines is not recommended (for yellow fever vaccine, see contraindications).
Caution is recommended when vinorelbine is used with strong inhibitors or inducers of cytochrome CYP3A4. Hence, the use of this medicine with phenytoin, fosphenytoin, itraconazole, ketoconazole or posaconazole is not recommended (see section 4.5).

Oral vinorelbine has been studied in patients with hepatic impairment at the following dosages:
- 60 mg/m² in patients with mild hepatic impairment (bilirubin <1.5 x ULN, and ALAT and/or ASAT between 1.5 and 2.5 x ULN);
- 50 mg/m² in patients with moderate hepatic impairment (bilirubin between 1.5 and 3 x ULN, whatever the levels of ALAT and ASAT).

The safety and pharmacokinetics of vinorelbine were not changed in these patients at the tested doses.

Oral vinorelbine has not been studied in patients with severe hepatic impairment, therefore the use in these patients is not recommended (see sections 4.2 and 5.2).

As there is a low level of renal excretion there is no pharmacokinetic rationale for reducing the dose of vinorelbine in patients with impaired kidney function (see sections 4.2 and 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

Common interactions for all cytotoxic agents

Concomitant use contraindicated (see section 4.3)
Yellow fever vaccine: risk of fatal generalised vaccine disease.

Concomitant use not recommended (see section 4.4)
Live attenuated vaccines (for yellow fever vaccine, see concomitant use contraindicated):: 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 when exists (poliomyelitis).

Phenytoin(and by extrapolation, fosphenytoin): risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic drug or loss of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin or fosphenytoin.
Interaction with special precaution for use:
Oral anticoagulant: There is an increased thrombotic and haemorrhagic risk in case of tumoral diseases. There is an eventuality of interaction between oral anticoagulants and anticancer chemotherapy. Increased frequency of the INR (International Normalised Ratio) monitoring is required.

+ Macrolides (clarithromycin, erythromycin, telithromycin)
Risk of increased toxicity of the anti-mitotic agent due to a reduction in its hepatic metabolism by clarithromycin, erythromycin or telithromycin. Close clinical and laboratory monitoring. Possibly, use an alternative antibiotic.

+Cobicistat
Increased neurotoxicity of the antimitotic due to a reduction in its hepatic metabolism by cobicistat. Close clinical monitoring and possible adjustment of dosage of the anti-mitotic agent.

Concomitant use to take into consideration
Ciclosporine, tacrolimus, everolimus, sirolimus: excessive immunodepression with risk of lymphoproliferation.
Interactions specific for vinca-alkaloids
Concomitant use is not recommended (see section 4.4)
Itraconazole, posaconazole, ketoconazole: increased neurotoxicity of vinca-alkaloids due to the decrease of their hepatic metabolism.

Interaction with special precaution for use :
Protease inhibitors: Increase of vinca-alkaloids toxicity due to the decrease of their hepatic metabolism.by protease inhibitors. Close clinical monitoring and eventually decrease of chemotherapy dosage is required.

Concomitant use to take into consideration (see section 4.8).
Mitomycin C: risk of bronchospams and dyspnoea are increased (see section 4.8)

As vinca-alkaloids are known as substrates for P-glycoprotein, and in the absence of specific study, caution should be exercised when combining vinorelbine with strong modulators of this membrane transporter.

Interactions specific for vinorelbine

The combination of vinorelbine with other drugs with known bone marrow toxicity is likely to exacerbate the myelosuppressive adverse effects.

There is no mutual pharmacokinetic interaction when combining vinorelbine with cisplatin over several cycles of treatment. However, the incidence of granulocytopenia associated with vinorelbine use in combination with cisplatin is higher than associated with vinorelbine single agent.

No clinically significant pharmacokinetic interaction was observed when combining vinorelbine 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 isoenzymes could increase blood concentration of vinorelbine and combination with strong inducers of this isoenzyme could decrease blood concentrations of vinorelbine.

Anti-emetic drugs such as 5HT3 antagonists (e.g. ondansetron, granisetron) do not modify the pharmacokinetics of vinorelbine soft capsules (see section 4.4).

In a phase I clinical study examining a combination of intravenous vinorelbine and lapatinib an increased incidence of grade 3/4 neutropenia was suggested. In this study the recommended dose of intravenous vinorelbine was 22.5 mg/m2 on days 1 and 8 every 3 weeks in combination with 1000 mg of lapatinib administered daily. This type of combination must therefore be administered with caution. Food does not modify the pharmacokinetics of vinorelbine.

4.6 Fertility, pregnancy and lactation

Pregnancy:
There are inadequate data on the use of vinorelbine in pregnant women. In reproductive studies conducted in animals, vinorelbine was embryotoxic and teratogenic (see section 5.3).
Based on the results of these animal studies and the pharmacological action of the medicinal product there is a potential risk of embryonic and foetal abnormalities.
Vinorelbine must not be used during pregnancy unless the expected individual benefit manifestly exceeds the potential risks.
If a patient becomes pregnant during treatment she must be informed of the risks to the unborn child and monitored carefully. The possibility of genetic counselling should also be considered.
Women of child-bearing potential:
Women of child-bearing potential must use effective contraception during treatment and up to 3 months after treatment.

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 cannot be excluded therefore breast feeding must be discontinued before starting treatment with vinorelbine (see section 4.3).

Fertility:
Men being treated with vinorelbine are advised not to father a child during and up to 3 months after treatment. 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

The overall reported frequency of undesirable effects was determined from clinical studies in 316 patients (132 patients with non-small cell lung cancer and 184 patients with breast cancer) who received the recommended regimen of vinorelbine (first three administrations at 60 mg/m²/week followed by 80 mg/m²/week).

Adverse reactions reported are listed below, by system organ and by frequency. Additional adverse reactions pooled from Post Marketing experience and clinical trials have been added according to the MedDRA classification with the frequency Not known.

The reactions were described using the NCI common toxicity criteria

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	Post marketing reports

Reactions were described using the W.H.O classification (grade 1=G1; grade 2=G2; grade 3=G3; grade 4=G4; grade 1-4=G1-4; grade 1-2=G1-2; grade 3-4=G3-4).

Undesirable effects reported with vinorelbine 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 is used as single agent or in combination with other chemotherapeutic such as cisplatin or capecitabinThe 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 G1-4: 12.7%; G3-4: 4.4%.
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 G3-4: 3.5%.
Not known:	Neutropenic sepsis; Complicated septicaemia and sometimes fatal. Severe sepsis sometimes with other organ failure Septicemia.

Blood and lymphatic system disorders

Very common:	Bone marrow depression resulting mainly in neutropenia G1-4: 71.5%; G3: 21.8%; G 4: 25.9%, is reversible and is the dose limiting toxicity. Leucopenia G1-4: 70.6%; G3: 24.7%; G4: 6%, Anemia G1-4: 67.4%; G3-4: 3.8%, Thrombocytopenia G1-2: 10.8%,
Common:	G4 Neutropenia associated with fever over 38°C including febrile neutropenia: 2.8%.
Not known:	Thrombocytopenia G3-4 Pancytopenia

Endocrine disorders

Not known:	Inappropriate antidiuretic hormone secretion (SIADH)

Metabolism and nutrition disorders

Very common:	Anorexia G1-2: 34.5%; G3-4: 4.1%
Not known:	Severe hyponatraemia

Psychiatric disorders

Common:	Insomnia: G1-2: 2.8%

Nervous system disorders

Very common:	Neurosensory disorders G1-2: 11.1 % were generally limited to loss of tendon reflexes and infrequently severe.
Common:	Neuromotor disorders G1-4: 9.2%: G3-4: 1.3%. Headache: G1-4: 4.1%, G3-4: 0.6%. Dizziness: G1-4: 6%; G3-4: 0.6%. Taste disorders: G1-2: 3.8%.
Uncommon:	Ataxia grade 3: 0.3%,

Eye disorders

Common:	Visual impairment G1-2: 1.3%

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 G1-4: 2.5%; G3-4: 0.3%; Arterial hypotension G1-4: 2.2%; G3-4: 0.6%

Respiratory system, thoracic and mediastinal disorders

Common:	Dyspnoea G1-4: 2.8%; G3-4: 0.3%. Cough: G1-2: 2.8%

Gastrointestinal disorders

Very Common:	Nausea G1-4: 74.7%; G3-4: 7.3%; Vomiting G1-4: 54.7%; G 3-4: 6.3%; supportive treatment (such as oral setrons) may reduce the occurrence of nausea and vomiting. Diarrhoea G1-4: 49.7 %; G3-4: 5.7%; Stomatitis G1-4:10.4 %; G3-4: 0.9%, Abdominal pain: G1-4: 14.2% Constipation G1-4: 19%; G3-4: 0.9% Prescription of laxatives may be appropriate in patients with prior history of constipation and /or who received concomitant treatment with morphine or morphine-mimetics. Gastric disorders: G1-4: 11.7%
Common:	Oesophagitis G1-3: 3.8%; G3: 0.3%, Dysphagia: G1-2: 2.3%
Uncommon:	Paralytic ileus G3-4: 0.9% [exceptionally fatal] treatment may be resumed after recovery of normal bowel mobility
Not known:	Gastrointestinal bleeding

Hepatobiliary disorders

Common:	Hepatic disorders: G1-2: 1.3%
Not known:	Transient elevations of liver function test

Skin and subcutaneous tissue disorders

Very common:	Alopecia usually mild in nature G1-2: 29.4% may occur.
Common:	Skin reactions G1-2: 5.7%

Musculoskeletal and connective tissue disorders

Common: Arthralgia including jaw pain,
Myalgia: G1-4: 7 %, G3-4: 0.3%

Renal and urinary disorders
Common: Dysuria G1-2: 1.6%
Other genitourinary disorders G1-2: 1.9%

General disorders and administration site conditions
Very common: Fatigue/malaise G1-4: 36.7 %; G3-4: 8.5 %;
Fever G1-4: 13.0%, G3-4: 12.1%
Common: Pain including pain at the tumour site G1-4: 3.8%, G3-4: 0.6%.
Chills: G1-2: 3.8%

Investigations
Very common: Weight loss G1-4: 25%, G3-4: 0.3%
Common: Weight gain G1-2: 1.3%

For the intravenous formulation of vinorelbine, the following additional Adverse Drug Reactions were reported: systemic allergic reactions, severe paresthesias, weakness of lower extremities, heart rhythm disorders, flushing, peripheral coldness, collapse, angina pectoris, bronchospasm, interstitial pneumopathy, pancreatitis, palmar-plantar erythrodysesthesia syndrome.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

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

Treatment
General supportive measures together with blood transfusion, growth factors and broad spectrum antibiotic therapy should be instituted as deemed necessary by the physician. There is no known antidote for overdosage of vinorelbine.
A close monitoring of hepatic function is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytotoxic antineoplastic belonging to the vinca alkaloid family, ATC Code: L01C A04

Mechanism of action
Vinorelbine is an 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 blocks mitosis at G2-M, causing cell death in interphase or at the following mitosis.

Paediatric population
Safety and efficacy of vinorelbine 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/m². 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 30mg/m^2, respectively of the IV form.

The blood exposure to vinorelbine increases proportionally with the dose up to 100 mg/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 (range: 7.5-39.7 l/kg), 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 sulphate 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/kg (range: 0.32-1.26 l/h/kg).

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 populations
Renal and liver impairment:
The effects of renal dysfunction on the pharmacokinetics of vinorelbine have not been studied. However, dose reduction in case of reduced renal function is not indicated with vinorelbine due to the low level of renal elimination.

Pharmacokinetics of orally administered vinorelbine were not modified after administration of 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) and of 50 mg/m² in patients with moderate liver impairment (bilirubin from 1.5 to 3 x ULN, whatever the levels of ALAT and ASAT). No data is available for patients with severe liver impairment, therefore vinorelbine is not recommended in these patients (see section 4.2 and 4.4).

Elderly

A study with oral vinorelbine in elderly patients (≥70 years) with NSCLC 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 (see section 4.2).

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

5.3 Preclinical safety data

Mutagenic and carcinogenic potential
The interaction of vinorelbine with the achromatic spindle during mitosis may lead to an incorrect distribution of chromosomes. In animal studies, intravenous vinorelbine caused aneuploidy and polyploidy. It is possible that vinorelbine may also have mutagenic effects (induction of aneuploidy) in humans.

Reproduction studies
In animal reproduction studies, vinorelbine has been shown to have embryolethal, fetolethal and teratogenic effects.

Pharmacological safety
No hemodynamic effect has been observed in dogs treated at the maximum tolerated dose; only non-significant minor repolarisation disorders appeared, as with the other vinca alkaloids tested. No effect on the cardiovascular system was observed in primates treated with repeated doses of vinorelbine for 39 weeks.

Animal overdosage
The symptoms of overdosage in the animals tested consisted of hair loss, abnormal behaviour (prostration, somnolence), pulmonary lesions, weight loss and varying degrees of bone marrow aplasia.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Macrogol 400
Polysorbate 80 (E433)
Purified water

Capsule shell:
Gelatin
Sorbitol liquid partially dehydrated (E420)
Titanium dioxide (E171)
Purified water
Vinorelbine Alvogen 20 mg and 80 mg soft capsules: Iron oxide yellow (E172)
Vinorelbine Alvogen 30 mg soft capsules: Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to outer carton.

6.4 Special precautions for storage

Please refer to outer carton.

6.5 Nature and contents of container

Carton box containing a PVC/PVDC-Al/PET/paper child-resistant blister.
Pack size: 1 or 4 blisters containing 1 soft capsule each. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Vinorelbine soft capsules is to be swallowed whole with water, without chewing or sucking on the capsule. It is recommended that the capsule be taken at the end of a meal.

Vinorelbine soft capsules is intended for oral administration only.

For safety reasons, any unused or damaged capsule should be returned to the physician or pharmacist to be destroyed according to the usual applicable procedure for cytotoxic substances.

7. PRODUCT OWNER

LOTUS INTERNATIONAL PTE. LTD.
80 Robinson Road, #02-00
Singapore 068898

8. DATE OF REVISION OF THE TEXT

04/2021