NAVELBINE®

1. NAME OF THE MEDICINAL PRODUCT

NAVELBINE® 20 mg soft capsule
NAVELBINE® 30 mg soft capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ACTIVE INGREDIENT	FORMULATION	
	20 mg	30 mg
Vinorelbine tartrate (mg)	27.70	41.55
Equivalent to vinorelbine (INN) base (mg)	20	30

Excipients with known effect: ethanol, sorbitol.
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

SOFT CAPSULE
20 mg soft capsule: light brown soft capsule printed N20
30 mg soft capsule: pink soft capsule printed N30

4. CLINICAL PARTICULARS

4.1 - Therapeutic indications

Non-small cell lung cancer - Advanced Breast Cancer

4.2 - Posology and method of administration

Navelbine® soft capsules must be given strictly by the oral route.
Navelbine® 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

60 mg/m² of body surface area, administered once weekly.

Subsequent administrations

Beyond the third administration, it is recommended to increase the dose of Navelbine® to 80 mg/m² once weekly except in those patients for whom the neutrophil count dropped once below 500/mm³ or more than once between 500 and 1000/mm³ during the first three administrations at 60 mg/m².

Neutrophil count during the first 3 administrations of 60 mg/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	80	60	60

• Dose Modification

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

Neutrophil count beyond the 4th administration of 80 mg/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 re-escalate 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 1000/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. The following table gives the dose required for appropriate ranges of body surface area (BSA).

	60 mg/m²	80 mg/m²
BSA (m²)	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 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 vinoreline (see section 5.2).

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

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

Administration in patients with renal insufficiency

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

4.3 - Contra-indications

- Known hypersensitivity to vinorelbine or other vinca alkaloids or to any of the constituent.
- 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.
- Patients requiring long-term oxygen therapy.
- Lactation (see section 4.6).
- In combination with yellow fever vaccine (see section 4.5).

4.4 - Special warnings and precautions for use

Special warnings
Navelbine® soft capsule should be prescribed by a physician 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 has 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 physician 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 $5HT_3$ antagonists setron (e.g. ondansetron, granisetron) may reduce the occurrence of this (see section 4.5).
Navelbine® soft capsule is associated with a higher incidence of nausea/vomiting than the IV 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.
Close haematological monitoring should 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 (see section 4.2).
- For dose escalation from 60 to 80 mg/m² per week, after the third administration please refer to section 4.2.
- For the administrations given at 80 mg/m², if the neutrophil count is below 500/mm³ or more than once between 500 and 1000 /mm³, the administration should not only be delayed but also reduced to 60 mg/m² per week. It is possible to re-escalate the dose from 60 to 80 mg/m² per week, please refer to section 4.2.

During clinical trials 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.
Use of this medicine with live attenuated vaccines is not recommended (for yellow fever vaccine, see contraindications).
Caution is recommended when Navelbine® 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).
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 medicine 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).
- with poor performance status.

Navelbine® should not be given concomitantly with radiotherapy if the treatment field includes the liver.
Oral Navelbine® 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 Navelbine® was not studied in patients with severe hepatic impairment, therefore its use is not recommended in these patients (see sections 4.2, 5.2).
As there is a low level of renal excretion there is no pharmacokinetic rationale for reducing the dose of Navelbine® in patients with impaired kidney function (see sections 4.2, 5.2).
The oral capsule and the intravenous injection are not bioequivalent.

4.5 - Interaction with other medicaments and other forms of interaction

Interctions common to all cytotoxics:

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 to vinca-alkaloids:

Concomitant use 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:
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 Navelbine® with strong modulators of this membrane transporter.

Interactions specific to vinorelbine:

The combination of Navelbine® with other drugs with known bone marrow toxicity is likely to exacerbate the myelosuppressive adverse effects.
There is no mutual pharmacokinetic interaction when combining Navelbine® with cisplatin over several cycles of treatment. However, the incidence of granulocytopenia associated with Navelbine® use in combination with cisplatin is higher than associated with Navelbine® single agent.
No clinically significant pharmacokinetic interaction was observed when combining Navelbine® 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 $5HT_3$ antagonists (e.g. ondansetron, granisetron) do not modify the pharmacokinetics of Navelbine® 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. Navelbine® 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 Navelbine® is excreted in human breast milk. The excretion of Navelbine® 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 Navelbine® (see section 4.3).
Fertility:
Men being treated with Navelbine® 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 patient treated with vinorelbine considering some adverse effects of the drug.

4.8 - Undesirable effects

The overall reported incidence 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 Navelbine® (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 Navelbine 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, diarrhea, stomatitis and constipation. Fatigue and fever were also reported very commonly.

Post-marketing experience:

Navelbine® 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, occasionally 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%; G4: 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: G3: 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] treatments 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: G 1-4: 7%, G3-4: 0.3%
- **Renal and urinary disorders**
  Common: Dysuria: G1-2: 1.6%
  Other genitourinary symptom: G1-2: 1.9%
- **General disorders and administration site conditions**
  Very common: Fatigue/malaise: G1-4: 36.7%; G3-4: 8.5%
  Fever: G 1-4: 13.0%, G3-4: 12.1%
  Common: Pain including pain at the tumour site: G 1-4: 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 Navelbine®, 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, acute respiratory distress syndrome.

4.9 - Overdose

Symptoms

Overdosage with Navelbine® could produce bone marrow hypoplasia sometimes associated with infection, fever and 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 is recommended.

Antidote

There is no known antidote for overdosage of Navelbine®.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: **Cytotoxic antineoplastic belonging to the vinca alkaloid family. ATC Code: L01CA04** (L - Antineoplastics and immunomodulators)

5.1 - Pharmacodynamic properties

Navelbine® (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.

Safety and efficacy of Navelbine® 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 dosing at 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/m² leads to blood exposure comparable to that achieved with intravenous vinorelbine at 25 and 30 mg/m² respectively of the IV form.

The blood exposure to vinorelbine increases proportionally with the dose up to 100 mg/m².

Interindividual variability of the exposure is similar after administration by IV 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 concentrations 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 CYP 3A4 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/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 patients groups

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 Navelbine® is not recommended in these patients (see section 4.2 and 4.4).

Elderly patients

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 Navelbine® soft capsule (see section 4.2).

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

Reproduction studies

In animal reproduction studies, Navelbine® 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

Fill solution: Ethanol anhydrous; purified water; glycerol; Macrogol 400.

Shell capsule: Gelatin, glycerol 85 %, anidrisorb 85/70 (D-sorbitol and 1 ,4-sorbitan), colouring agent E172 and E171 (red or yellow according to each strength), medium chain triglycerides, PHOSAL 53 MCT (phosphatidylcholine, glycerides, ethanol).

Edible printing ink: E120, hypromellose, propyleneglycol.

6.2 - Incompatibilities: Not applicable

6.3 - Shelf life: 36 months for 20 mg and 30 mg

6.4 - Special precautions for storage: Store between + 2°C and +8°C (in refrigerator). Store in the original container.

Keep the immediate packaging tightly closed.

6.5 - Nature and contents of container:

Not all strengths are marketed.

PVC/PVDC/child resistant aluminium blister.

Pack size: 1 capsule.

6.6 - Special precautions for disposal and Other Handling

Navelbine® 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.

Navelbine® 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.

Instructions for use and handling of Navelbine® soft capsules:

To open the tamper-proof packaging:

- Cut the blister with scissors along the black line.
- Gently peel back the white film covering the blister.
- Press on the clear plastic to push the capsule through the aluminium foil.

For precautions for use, see section 4.4.

7. MANUFACTURER

CATALENT GERMANY EBERBACH GMBH
Gammelsbacher Strasse2
69412 Eberbach, GERMANY

8. PRODUCT OWNER & MARKETING AUTHORISATION HOLDER

PIERRE FABRE MEDICAMENT, France

9. PRODUCT REGISTRANT

ORIENT EUROPHARMA PTE. LTD.
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10. DATE OF (PARTIAL) REVISION OF THE TEXT

Month YYYY

Licence PIERRE FABRE MEDICAMENT

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Client :	PIERRE FABRE
Date de création :	07-01-2022
Demande de :	Alexandra
Produit :	NAVELBINE oral
Pays :	SINGAPOUR (1L)
Format :	250 x 300 mm (75000 mm²) - a4
Code article :	**mock-up**
Couleurs :	noir
Texte :	futura std : 7,5 pts - 85% interlignage : 8,5 pts nb de signes : 29700
Epreuves :	v2 : 07-02-2022
	v3 : 09-02-2022 (format sticker)
	v4 : 14-02-2022 (inversion r°v°)
Hors estimation :	v5 : 15-02-2022 (rotation texte 90°) horaire)
	v6 : 17-10-2022

Clôturé le :

Préalablement à toute livraison par la société OPTION K à son client de maquettes en version fichiers natifs, fichiers PDF haute définition ou tout autre type de fichier utile, la société OPTION K émet un BAT (Bon à tirer) que le client s'engage à signer. La validation du BAT par le client décharge en conséquence OPTION K de toute responsabilité.
S'agissant ensuite de toute impression définitive des maquettes qui auront été livrées par la société OPTION K à son client, ledit client s'engage à signer un bon à tirer émanant de l'imprimeur qu'il aura choisi. En l'absence de BAT/imprimeur signé par le client ou en cas de validation dudit BAT/imprimeur par lui, aucune responsabilité de la société OPTION K ne pourra être mise à charge.

VALIDATION CLIENT