1. NAME OF THE MEDICINAL PRODUCT
NAVELBINE 20 mg, soft capsules
NAVELBINE 30 mg, soft capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Vinorelbine 20.00 mg/30.00 mg
As vinorelbine ditartrate 27.70 mg/41.55 mg for one soft capsule
Excipients with known effect: ethanol, sorbitol
For the 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
Oral NAVELBINE is indicated as single-agent and in combination chemotherapy in the treatment of:
- Non-small cell lung cancer
- Metastatic breast cancer

4.2 Posology and method of administration
- 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.

<table>
<thead>
<tr>
<th>Neutrophil count during the first 3 administrations of 60 mg/m²/week</th>
<th>Neutrophils &gt;1000</th>
<th>Neutrophils ≥500 and &lt;1000 (1 episode)</th>
<th>Neutrophils ≥500 and &lt;1000 (2 episodes)</th>
<th>Neutrophils &lt;500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended dose starting with the 4th administration</td>
<td>80</td>
<td>80</td>
<td>60</td>
<td>60</td>
</tr>
</tbody>
</table>

Dose modification
For any administration planned to be 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 be delayed until recovery and the dose reduced from 80 to 60 mg/m² per week during the 3 following administrations.

<table>
<thead>
<tr>
<th>Neutrophil count beyond the 4th administration of 80 mg/m²/week</th>
<th>Neutrophils &gt;1000</th>
<th>Neutrophils ≥500 and &lt;1000 (1 episode)</th>
<th>Neutrophils ≥500 and &lt;1000 (2 episodes)</th>
<th>Neutrophils &lt;500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended dose starting for the next administration</td>
<td>80</td>
<td>60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

### Administration

Navelbine must be given strictly by the oral route. Navelbine should be swallowed with water without chewing or sucking the capsule. It is recommended to take the capsule with some food.

### Administration in the 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).

### 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/m$^2$/week in patients with mild hepatic disorder (bilirubin $<1.5 \times$ ULN, and ALT and/or AST between 1.5 and 2.5 × ULN). In patients with moderate hepatic disorder (bilirubin between 1.5 and 3 × ULN, independent of ALT and AST), Navelbine need to be administered at a dose of 50 mg/m$^2$/week. A administration of Navelbine to patients with severe hepatic disorder is not recommended because there is insufficient data in this population in order to determine the pharmacokinetics, efficacy and safety (see sections 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 the use and handling of oral NAVELBINE (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 $<1500/mm^3$ or severe infection current or recent (within 2 weeks).
- Platelet count $< 100000/mm^3$
- 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 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 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 5HT3 antagonists (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 i.v formulation. A primary prophylaxis with antiemetics is recommended. 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).

This medicinal product contains small amounts of ethanol (alcohol), less than 100 mg per dose.
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 see 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 reescalate the dose from 60 to 80 mg/m² per week, (see 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 or posaconazole is not recommended (see section 4.5).

Special precautions for use
Special care should be taken when prescribing for patients
- With history of ischaemic 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 has been studied in patients with hepatic disorder at the following dosages:
- 60 mg/m² in patients with mild hepatic disorder (bilirubin <1.5 x ULN, and ALT and/or AST from 1.5 to 2.5 x ULN);
- 50 mg/m² in patients with moderate hepatic disorder (bilirubin between 1.5 and 3 x ULN, independent of ALT and AST level).

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

Oral Navelbine has not been studied in patients with severe hepatic disorder, therefore the use in these patients is not recommended (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 4.1, 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

Interactions 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, fosphenytoïn): 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.

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: 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 5HT3 antagonists (e.g. ondansetron, granisetron) do not modify the pharmacokinetics of Navelbine soft capsules (see section 4.4).
An increased incidence of grade 3/4 neutropenia has been suggested when intravenous vinorelbine and lapatinib were associated in one clinical phase I study. In this study, the recommended dose of intravenous form of vinorelbine in a 3-weekly schedule on day 1 and day 8 was 22.5 mg/m² when combined with daily lapatinib 1000 mg. This type of combination should be administered with caution.
Food does not modify the pharmacokinetics of vinorelbine.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy:**
There are insufficient data available on the use of vinorelbine in pregnant women. Studies in animals have shown embryotoxicity and teratogenicity (see section 5.3). On the basis of the results of animal studies and the pharmacological action of the medicinal product, there is a potential risk of embryonic and foetal abnormalities.
Navelbine should therefore not be used during pregnancy, unless the individual awaited benefit clearly outweighs the potential risks. 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 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 can not 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 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 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 from Post Marketing experience have been added according to the MedDRA classification with the frequency Not known.

The reactions were described using the NCI common toxicity criteria

<table>
<thead>
<tr>
<th>Very common</th>
<th>≥1/10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>≥1/100, &lt;1/10</td>
</tr>
<tr>
<td>Uncommon</td>
<td>≥1/1,000, &lt;1/100</td>
</tr>
<tr>
<td>Rare</td>
<td>≥1/10,000, &lt;1/1,000</td>
</tr>
<tr>
<td>Very rare</td>
<td>&lt;1/10,000</td>
</tr>
<tr>
<td>Not known</td>
<td>Post marketing reports</td>
</tr>
</tbody>
</table>

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 agents such as cisplatin or capecitabin.
The most commonly system organ classes involved during post-marketing experience are: ‘Blood and lymphatic system disorders’, ‘Gastrointestinal disorders’ 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

• 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%.

• Metabolism and nutrition disorders

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:**
- 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 disorders 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:**
- Hypertension G1-4: 2.5%; G3-4: 0.3%
- 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%

- Anorexia G 1-4: 38.6%; G 3-4: 4.1%
- 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%

**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 disorders 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%

**Undesirable effects with Navelbine, concentrate for infusion:**

Some undesirable effects were observed with Navelbine, solution for infusion during pre- and post-marketing experience which were not reported with Navelbine soft capsule:

In order to provide the complete information and to further the safety of use of Navelbine soft capsule, these effects are presented below:

- **Infections and Infestations**
  Uncommon: Septicemia (very rarely fatal)

- **Immune system disorders**
  Not known: Systemic allergic reactions as anaphylaxis, anaphylactic shock or anaphylactoid type reactions

- **Endocrine disorders**
  Not known: Inappropriate antidiuretic hormone secretion (SIADH)

- **Vascular disorders**
  Uncommon: Flushing and peripheral coldness
  Rare: Severe hypotension, collapse

- **Respiratory system, thoracic and mediastinal disorders**
  Uncommon: Bronchospasm may occur as with other vinca alkaloids.
  Rare: Interstitial pneumopathy has been reported (sometimes fatal)

- **Gastrointestinal disorders**
  Rare: Pancreatitis

**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 listed in Appendix V.

**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**

**5.1 Pharmacodynamic properties**
Pharmacotherapeutic group: Vinca alkaloids and analogues (ATC Code: L01C A04)

Navelbine 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.

Navelbine 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. Clinical data from two single arm Phase II studies using intravenous vinorelbine in 33 and 46 paediatric patients with recurrent solid tumors, including rhabdomyosarcoma, other soft tissue sarcoma, Ewing sarcoma,
liposarcoma, synovial sarcoma, fibrosarcoma, central nervous system cancer, osteosarcoma, neuroblastoma at doses of 30 to 33.75 mg/m² D1 and D8 every 3 weeks or once weekly for 6 weeks every 8 weeks, showed no meaningful clinical activity. The toxicity profile was similar to that reported in adult patients (section 4.2).

5.2 Pharmacokinetic properties
Pharmacokinetic parameters of vinorelbine were evaluated in blood.

Absorption
After oral administration, vinorelbine is rapidly absorbed and the T\text{max} is reached between 1.5 to 3 h with a blood concentration peak (C\text{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/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 21.21 kg⁻¹ (range: 7.5 - 39.71 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 CYP 3A4 isofrom 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 hepatic disorder (bilirubin <1.5 x ULN, and ALT and/or AST 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 ALT and AST). No data are available for patients with severe hepatic disorder, therefore the use of Navelbine is not recommended (see section 4.2, 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).

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 NAVELBINE with the achromatic
6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store between + 2°C and + 8°C (in refrigerator).
Keep the immediate packaging tightly closed.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>
1 capsule in a blister (PVC/PVDC/Aluminium).

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. MARKETING AUTHORISATION HOLDER
PIERRE FABRE MEDICAMENT
45 Place Abel Gance
92100 Boulogne
FRANCE

8. MARKETING AUTHORISATION NUMBER(S)
365 948-4 : 1 capsule of 20 mg in a blister (PVC/PVDC/Aluminium).
365 949-0 : 1 capsule of 30 mg in a blister (PVC/PVDC/Aluminium).
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorisation: 22 January 2001
Date of latest renewal: 22 February 2006

10. DATE OF REVISION OF THE TEXT
October 2013

CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE
List I.
Medicinal product subject to hospital prescription. Prescription reserved for specialists in oncology or in haematology, or for physicians with experience in cancerology. Medicinal product requiring specific monitoring during treatment. An information and monitoring booklet intended for the patient is provided by the marketing authorisation holder.