SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

[Product Name] 20 mg Soft Capsules
[Product Name] 30 mg Soft Capsules
[Product Name] 80 mg Soft Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains vinorelbine tartrate equivalent to 20 mg vinorelbine
Each soft capsule contains vinorelbine tartrate equivalent to 30 mg vinorelbine
Each soft capsule contains vinorelbine tartrate equivalent to 80 mg vinorelbine

Excipient(s) with known effect:
Each soft capsule containing 20 mg vinorelbine contains 10.54 mg sorbitol.
Each soft capsule containing 30 mg vinorelbine contains 15.96 mg sorbitol.
Each soft capsule containing 80 mg vinorelbine contains 29.35 mg sorbitol.

Each soft capsule containing 20 mg vinorelbine contains 5 mg ethanol.
Each soft capsule containing 30 mg vinorelbine contains 7.5 mg ethanol.
Each soft capsule containing 80 mg vinorelbine contains 20 mg ethanol.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsules, soft
20 mg soft capsule: An oval-shaped light brown soft capsule with a size of 9.0mm x 7.0mm with black "20" printed on the surface
30 mg soft capsule: An oblong-shaped pink soft with a size of 15.0mm x 6.0mm capsule with black "30" printed on the surface
80 mg soft capsules: An oblong-shaped pale yellow soft capsule with a size of 20.0mm x 8.0mm with black "80" printed on the surface.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-small cell lung cancer
Advanced breast cancer

4.2 Posology and method of administration

Adults

- **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 [Product Name] to 80 mg/m² once weekly except in those patients for whom the neutrophil count dropped once below 500/mm^3 or more than once between 500 and 1000/mm^3 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/mm^3 or more than once between 500 and 1000/mm^3, 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/m^2 per week if the neutrophil count did not drop below 500/mm^3 or more than once between 500 and 1000/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's convenience.

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

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.

Special population

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 impairment
Vinorelbine can be administered at the standard dose of 60 mg/m²/week in patients with mild hepatic disorder (bilirubin < 1.5 x ULN, and ALT and/or AST between 1.5 to 2.5 x ULN). In patients with moderate hepatic disorder (bilirubin between 1.5 and 3 x ULN, independent of ALT and AST), [Product Name] needs to be administered at a dose of 50 mg/m²/week. Administration of vinorelbine 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).

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

Method of administration
[Product Name] must be given strictly by the oral route.
Capsules [Product Name] should be swallowed with water without chewing or sucking the capsule because the liquid inside is an irritant and may be harmful if it comes into contact with your skin, eyes or mucosa. It is recommended to take the capsule with some food.

Specific instructions must be followed for the administration of vinorelbine (see section 6.6)

4.3 Contraindications

- Known hypersensitivity to vinorelbine or other vinca alkaloids or to any of the constituents mentioned in section 6.1.
- 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
- 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
[Product Name] 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 $5HT_3$ antagonists (e.g. ondansetron, granisetron) may reduce the occurrence of this (see section 4.5).
[Product Name] 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.
This medicinal product contains small amounts of ethanol (alcohol), less than 100 mg per dose.

This medicine contains 5 mg of alcohol (ethanol) in each 20 mg soft capsule which is equivalent to 2.85%. The amount in 20 mg dose of this medicine is equivalent to less than 1 ml beer or 1 ml wine.

This medicine contains 7.5 mg of alcohol (ethanol) in each 30 mg soft capsule which is equivalent to 2.85%. The amount in 30 mg dose of this medicine is equivalent to less than 1 ml beer or 1 ml wine.

This medicine contains 20 mg of alcohol (ethanol) in each 80 mg soft capsule which is equivalent to 2.85%. The amount in 80 mg dose of this medicine is equivalent to less than 1 ml beer or 1 ml wine.

The small amount of alcohol in this medicine will not have any noticeable effects.

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 $1500/mm^3$ and/or the platelet count is below $100000/mm^3$, then the treatment should be delayed until recovery.
- For dose escalation from 60 to 80 mg/m^2 per week, after the third administration please refer see section 4.2.
- For the administrations given at 80 mg/m^2, if the neutrophil count is below $500/mm^3$ or more than once between 500 and $1000/mm^3$, the administration should not only be delayed but also reduced to 60 mg/m^2 per week. It is possible to re-escalate the dose from 60 to 80 mg/m^2 per week, please 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 80 mg/m^2 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.

Special precautions for use

Special care should be taken when prescribing for patients
- with a history of ischaemic heart disease (see section 4.8).
- with poor performance status

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

This medicinal product is specifically contra-indicated with yellow fever vaccine and its concomitant use with other live attenuated vaccines is not recommended. Caution must be exercised when combining [Product Name] and strong inhibitors or inducers of CYP3A4 (see section 4.5), and its combination with phenytoin (like all cytotoxics) and with itraconazole (like all vinca alkaloids) is not recommended.
Capsules [Product Name] 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. Vinorelbine capsules have not been studied in patients with severe hepatic disorder, therefore the use in these patients is not recommended (see sections 4.1 and 5.2).

As there is a low level of renal excretion there is no pharmacokinetic rationale for reducing the dose of [Product Name] in patients with impaired kidney function (see sections 4.1 and 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

Interactions common to all cytotoxics:
Due to the increase of thrombotic risk in case of tumoral diseases, the use of anticoagulative treatment is frequent. The high intra-individual variability of the coagulability during diseases, and the eventuality of interaction between oral anticoagulants and anticancer chemotherapy required, if it is decided to treat the patient with oral anticoagulants, to increase frequency of the INR (International Normalised Ratio) monitoring.

Concomitant use contraindicated:
Yellow fever vaccine : risk of fatal generalised vaccine disease.

Concomitant use not recommended:
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 vaccine when one exists (poliomyelitis).

Phenytoin: risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic medicinal products or loss of efficacy of the cytotoxic medicinal products due to increased hepatic metabolism by phenytoin.

- Concomitant use to take into consideration:

Ciclosporine, tacrolimus: excessive immunodepression with risk of lymphoproliferation.

Interactions specific to vinca-alkaloids:

Concomitant use not recommended:
Itraconazole: increased neurotoxicity of vinca-alkaloids due to the decrease of their hepatic metabolism.

Concomitant use to take into consideration:
Mitomycin C: risk of bronchospasm and dyspnoea are increased, in rare case an interstitial pneumonitis was observed

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

Interactions specific to vinorelbine

The combination of [Product Name] with other medicinal products 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 in combination with cisplatin was higher than the one associated with vinorelbine single agent.

No clinically significant pharmacokinetic interaction was observed when combining [Product Name] with several other chemotherapeutic agents (paclitaxel, docetaxel, capecitabine and oral cyclophosphamide).

As CYP 3A4 is mainly involved in the metabolism of vinorelbine, combination with strong inhibitors of this isoenzyme (e.g. ketoconazole, 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 [Product Name] 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/m^2 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.
Vinorelbine 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 for at least 7 months after treatment.

Breastfeeding
It is unknown whether vinorelbine is excreted in human 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 [Product Name] (see section 4.3).

Fertility
Men being treated with [Product Name] are advised not to father a child during and for at least 4 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

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	Cannot be estimated from the available data

Undesirable effects reported with [Product Name] 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:
[Product Name] soft capsule is used as single agent or in combination with other chemotherapeutic or targeted therapy agents such as cisplatin or capecitabine.
The most commonly involved system organ classes 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 Severe sepsis sometimes with other organ failure Septicaemia

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%, Anaemia 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%
Not known:	Posterior reversible encephalopathy syndrome

Eye disorders

Common:	Visual impairment G1-2: 1.3%

Cardiac disorders

Uncommon:	Heart failure, 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, thoracic and mediastinal disorders

Common:	Dyspnoea G1-4: 2.8%; G3-4: 0.3%. Cough: G1-2: 2.8%
Not known:	Pulmonary embolism

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 tests

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 vinorelbine, the following additional adverse drug reactions were reported: systemic allergic reactions, severe paraesthesias, weakness of lower extremities, heart rhythm disorders, flushing, peripheral coldness, collapse, angina pectoris, bronchospasm, interstitial pneumopathy, pancreatitis, palmar-plantar erythrodysaesthesia syndrome. acute respiratory distress 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 the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Overdosage with [Product Name] 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 is recommended.

Antidote
There is no known antidote for overdosage of [Product Name]**.**

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vinca alkaloïds and analogues
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 spiralisation 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
The safety and efficacy of [Product Name]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_{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/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 concentration up to a 300-fold higher 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 populations

Renal and hepatic 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/m^2 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/m^2 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 contra-indicated in these patients (see section 4.3).

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 [Product Name] soft capsule (see section 4.2).

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

5.3 Preclinical safety data

Vinorelbine induced chromosome damages but was not mutagenic in Ames test.

It is assumed that vinorelbine can cause mutagenic effects (induction aneuploidy and polyploidy) in man.

In animal reproductive studies, vinorelbine was embryo-foeto-lethal and teratogenic.

No haemodynamic effects were found in dogs receiving vinorelbine at maximal tolerated dose; only some minor, non significant disturbances of repolarisation were found as with other vinca alkaloids tested.
No effect on the cardiovascular system was observed in primates receiving repeated doses of vinorelbine over 39 weeks.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule filling:
anhydrous ethanol
purified water
glycerol
macrogol 400

Capsule cover:
gelatin
glycerol
partially dehydrated sorbitol liquid
titanium dioxide (E171)
purified water
[Product Name] 20 mg and 80 mg Soft Capsules- iron oxide yellow (E172)
[Product Name] 30 mg Soft Capsules-iron red oxide (E172)

Other ingredients:
printing ink (Nonvolatile component-shellac glaze, black iron oxide (E172), propylene glycol)
medium chain triglycerides

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a refrigerator (at 2°C - 8°C) in the original package to protect from light.

6.5 Nature and contents of container

PVC / PVDC / aluminum blister pack.
The soft capsules are packed in a child-resistant blister pack.

Pack Size:

[Product Name] 20 mg Soft Capsules:	Pack of 1 blister with 1 soft capsule. Pack of 4 blisters with 1 soft capsule each
[Product Name] 30 mg Soft Capsules:	Pack of 1 blister with 1 soft capsule. Pack of 4 blisters with 1 soft capsule each
[Product Name] 80 mg Soft Capsules:	Pack of 1 blister with 1 soft capsule.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

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

7. MARKETING AUTHORISATION HOLDER
[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF AUTHORISATION
<Date of first authorization: {DD month YYYY} >
<Date of latest renewal: {DD month YYYY}>
[To be complete nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}
[To be completed nationally]