ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NAVELBINE 20 mg, soft capsule

NAVELBINE 30 mg, soft capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vinorelbine..... 20.00 mg

As vinorelbine ditartrate..... 27.70 mg

Per soft capsule.

Vinorelbine..... 30.00 mg

As vinorelbine ditartrate..... 41.55 mg

Per soft capsule.

Excipients with known effect: ethanol, sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsule

20mg: Light brown soft capsule, printed N20

30mg: Pink coloured soft capsule, printed N30

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Oral NAVELBINE is indicated for use as monochemotherapy and in combination chemotherapy in

- non-small cell lung cancer
- metastatic breast cancer
-

4.2. Posology and method of administration

- **Monotherapy:**

The recommended administration regimen is as follows:

First three administrations:

Dose 60 mg/m^2 body surface area, administered once per week.

Subsequent administrations:

Beyond the third administration it is recommended that the dose of NAVELBINE soft capsule be increased to 80 mg/m^2 once weekly except for patients whose neutrophil count has fallen once below

500/mm^3 or more than once to between 500 and 1000/mm^3 during the first three dose administrations at 60 mg/m^2.

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

Dose modification

For any planned administration at the dose of 80 mg/m^2, if the neutrophil count is below 500/mm^3 or has been between 500 and 1000/mm^3 more than once, administration should be delayed until this parameter has returned to normal and the dose be reduced from 80 to 60 mg/m^2 per week for the subsequent 3 administrations.

Neutrophil count BEYOND THE 4th ADMINISTRATION **At 80mg/m²/Week**	**Neutrophils > 1000**	**Neutrophils ≥ 500 and < 1000 (1 episode)**	**Neutrophils ≥ 500 and < 1000** **(2 episodes)**	**Neutrophils < 500**
Recommended dose for the next administration	80		60	

It is possible to increase the dose from 60 to 80 mg/m² per week if the neutrophil count is not below 500/mm^3 or between 500 and 1000/mm^3 on more than one occasion during the last three administrations at 60 mg/m², consistent with the rules described for the first three administrations.

- **In combination chemotherapy the dose and treatment regimen should be adjusted according to the treatment protocol**

Clinical trial results show that an oral dose of 80 mg/m^2 is equivalent to an IV dose of 30 mg/m^2 and that an oral dose of 60 mg/m^2 is equivalent to an IV dose of 25 mg/m^2.

This is based on combination protocols alternating between the IV and oral form which improve patient comfort.

For combination protocols the dose and treatment regimen should be adjusted according to the treatment protocol.

Even for patients with a BSA of > 2 m^2, the total dose must never exceed 120 mg per week (60 mg/m^2 dosage) or 160 mg per week (80 mg/m^2 dosage).

Administration

NAVELBINE must be administered orally strictly.

Navelbine soft capsule must be swallowed with water without chewing or sucking the capsule.

It is recommended that the capsule be taken at the end of a meal.

Administration in the elderly:

Clinical experience has not established any significant differences in elderly patients in terms of response rate, although it is not possible to exclude greater sensitivity in some of these patients. Age does not change the pharmacokinetics of vinorelbine.

Administration in children:

The safety and efficacy have not been studied in children and as a result administration of Navelbine is not recommended (see section 5.1).

Administration in patients suffering from liver insufficiency:

Navelbine can be administered at the standard dose of 60 mg/m² per week in patients suffering from mild hepatic disorder (bilirubin < 1.5 x ULN and AST and/or ALT 1.5 to 2.5 x ULN).

In patients suffering from moderate hepatic disorder (bilirubin 1.5 to 3 x ULN regardless of the ALT and AST), Navelbine should be administered at a dose of 50 mg/m²/week. Administration of Navelbine to patients with severe hepatic disorder is not recommended as there is insufficient data to determine the pharmacokinetics, efficacy and safety of Navelbine in this population (see sections 4.4, and 5.2)

Administration in patients suffering from renal insufficiency:

As renal excretion is low, there is no pharmacokinetic justification to reduce the dose of Navelbine in patients with renal insufficiency (see section 4.4 and 5.2).

Instructions for use and handling of oral Navelbine (see section 6.6).

4.3. Contraindications

- Known hypersensitivity to vinorelbine or other vinca alkaloids or to any other constituent.
- Disease significantly affecting absorption.
- History of significant surgery resection of the stomach or small bowel.
- Neutrophil count under 1500/mm^3 or severe current or recent infection (within 2 weeks).
- Platelet count < 100000/mm^3.
- Patients requiring long term oxygen therapy.
- Lactation (See section 4.6)
- In combination with the yellow fever vaccine (see section 4.5).

4.4. Special warnings and precautions for use

Special warnings

Navelbine soft capsules must be prescribed only by a physician who is qualified and experienced in the use of chemotherapy with facilities for monitoring cytotoxic drugs.

The liquid content is irritant if the patient chews or sucks the capsule in error. Rinse the mouth with water or preferably physiological saline solution.

If a capsule being cut or damaged, its liquid content which has irritating properties may have adverse reactions if it comes into contact with the skin, mucosal membranes or eyes.

Damaged capsules must not be swallowed and should be returned to the pharmacist or physician in order to be destroyed appropriately.

In the event of contact, immediately wash thoroughly with water or preferably physiological saline solution.

If vomiting occurs during the hours after taking the medicine, never repeat administration of the dose. Symptomatic treatment such as 5HT3 antagonists (for example: ondansetrons, granisetrons) may reduce the occurence of vomiting (see section 4.5).

Navelbine soft capsule is associated with a higher incidence of nausea or vomiting than the injectable form. Prophylactic anti-emetic treatment is recommended.

As it contains sorbitol, patients with rare hereditary problems of fructose intolerance should not take Navelbine soft capsule.

Treatment must be administered under strict haematological monitoring (blood haemoglobin, leukocyte, neutrophil and platelet count should be checked each day the substance is administered).

This medicinal product contains small amounts of ethanol (alcohol), less than 100 mg per dose.

The dose administered should be determined according to the haematology profile:

- If the neutrophil count is under 1500/mm^3 and/or the platelet count is under 100000/mm^3, treatment should be deferred until these parameters have returned to normal and the patient should be monitored (see section 4.2).
- Refer to section 4.2 for increasing the 60 mg/m² dose to 80 mg/m^2 per week after the third dose has been administered.
- For administrations at the 80 mg/m^2 dose, if the neutrophil count is under 500/mm^3 or between 500 and 1000/mm^3, on more than one occasion, administration should not only be delayed but the dose should be reduced to 60 mg/m^2 per week. The 60 mg/m² dose can be increased again to 80 mg/m^2 per week (see section 4.2).

In clinical trials in which treatments were started at a dose of 80 mg/m^2, a few patients developed complications involving excessive neutropenia. This included patients with a poor performance status.

It is therefore recommended that treatment be started at the dose of 60 mg/m^2 and then increased to 80 mg/m^2 if the initial dose is well tolerated, as described in section 4.2.

Further investigations should be performed without delay if patients have signs or symptoms suggestive of infection.

Use of this medicinal product in combination with a live attenuated vaccine is not recommended (for the yellow fever vaccine, see contraindications).

Caution is recommended when Navelbine is used at the same time as potent cytochrome CYP3A4 inhibitors or inductors. Hence, taking this medicinal product with phenytoin, fosphenytoin, itraconazole, ketoconazole or posaconazole is not recommended (see section 4.5).

Special precautions for use

Special precautions are recommended in patients with:

- History of ischaemic heart disease (see section 4.8).
- Poor performance status.

Navelbine soft capsule should not be given concomitantly with radiotherapy if the treatment fields include the liver.

Navelbine soft capsule has been studied in patients suffering from hepatic disorder at the following doses:

- 60 mg/m²/week in patients suffering from mild hepatic disorder (bilirubin < 1.5 x ULN, ALT and/or AST 1.5 to 2.5 x ULN).
- 50 mg/m²/week in patients suffering from moderate hepatic disorder (bilirubin 1.5 to 3 x ULN, regardless of the ALT or AST level).

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

Navelbine soft capsule has not been studied in patients suffering from severe hepatic disorder and its use is therefore not recommended in these patients (see sections 4.2 and 5.2).

As renal excretion is low, there is no pharmacokinetic justification to reduce the dose of Navelbine in patients with impaired kidney function (see section 4.2,5.2).

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 (see Concomitant use contraindicated for the yellow fever vaccine):
Risk of generalised, potentially fatal, vaccine disease. This risk is increased in subjects who are already immunodepressed due to the underlying disease. Use an inactivated vaccine when this exists (poliomyelitis).

+ Phenytoin (and, by extrapolation, fosphenytoin):
Risk of seizures due to reduced gastrointestinal absorption of phenytoin alone due to the cytotoxic or loss of efficacy of the cytotoxic agent due to an increase in its hepatic metabolism by phenytoin or fosphenytoin.

Concomitant use requiring precautions

+ Vitamin K antagonists
Increased risk of thrombosis and haemorrhage in tumour disease. In addition, possible interaction between the VKA and chemotherapy. More frequent monitoring of the INR.

+ 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

+ Immunosuppressants (ciclosporin, everolimus, sirolimus, tacrolimus):
Excessive immunosuppression with risk of lymphoproliferative syndrome.

INTERACTIONS SPECIFIC TO THE VINCA ALKALOIDS

Concomitant use not recommended (see section 4.4)

+ Itraconazole, posaconazole, ketoconazole:
Increased neurotoxicity of the anti-mitotic agent due to a reduction in its hepatic metabolism by itraconazole, ketoconazole or posaconazole.

Concomitant use requiring precautions

+ Protease inhibitors
Increased toxicity of the antimitotic due to a reduction in its hepatic metabolism by the protease inhibitor. Close clinical monitoring and possible adjustment of dosage of the anti-mitotic agent.

Concomitant use to take into consideration

+ Mitomycin C:
Risk of increased pulmonary toxicity of mitomycin and the vinca alkaloids (see section 4.8).

+ As the vinca alkaloids are recognised to be substrates for glycoprotein P and in the absence of specific studies, precautions are required when Navelbine is used in combination with potent membrane transport modulators.

INTERACTIONS SPECIFIC TO VINORELBINE

Combination of Navelbine with other medicinal products known to have bone marrow toxicity is liable to worsen the myelosuppressive adverse effects.

There are no mutual pharmacokinetic interactions when Navelbine is used in combination with cisplatin during several treatment cycles. The incidence of granulocytopenias however was greater with combination of Navelbine with cisplatin than when Navelbine was used in monotherapy.

No clinically significant pharmacokinetic interactions have been seen during combination of Navelbine with several other anti-cancer agents (paclitaxel, docetaxel, capecitabine and oral ciclophosphamide).

As CYP3A4 is mostly involved in the metabolism of vinorelbine, combination with potent inhibitors of this isoenzyme may increase blood vinorelbine concentration and combination with potent inducers of this isoenzyme may reduce the blood concentration of vinorelbine.

Anti-emetics such as the 5HT3 antagonists (for example: ondansetron, granisetron) do not result in changes in the pharmacokinetics of Navelbine soft capsule (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/m^2 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.

Interaction with foods: simultaneous ingestion of food does not change exposure to 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 be using an effective contraception during treatment and for three months after treatment is stopped.

Lactation

It is not known whether Navelbine is excreted into human breast milk.

The excretion of Navelbine into milk has not been studied in animals.

It is not possible to exclude a risk during breastfeeding. As a result, breastfeeding must be stopped before beginning treatment with Navelbine (see section 4.3).

Fertility

Men treated with Navelbine must be warned not to conceive a child during treatment and for at least 3 months after treatment.

Before treatment it is recommended that sperm storage be considered because of the risk of irreversible infertility following treatment with vinorelbine.

4.7. Effects on ability to drive or use machines.

No studies on the ability to drive or use machines have been conducted although, based on its pharmacodynamic profile, vinorelbine does not affect these activities. Caution, however, is required in patients treated with vinorelbine because of the adverse effects due to this medicinal product.

4.8. Undesirable effects:

The overall incidence of adverse reactions has been established from clinical studies in which 316 patients (132 patients suffering from NSCLC and 184 patients suffering from breast cancer) received the recommended protocol for Navelbine soft capsule (first three administrations at a dose of 60 mg/m²/week followed by administrations at a dose of 80 mg/m²/week).

The adverse reactions reported have been listed below by system organ class and incidence. The additional adverse reactions found from post-marketing experience have been added with unknown incidence consistent with the MedDRA classification.

The reactions are defined as follows using the NCI CTC severity grades.

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
Unknown	Post-marketing cases reported

The reactions are described using the WHO 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).

Adverse reactions reported with Navelbine soft capsule

Pre-marketing experience:

The most commonly reported adverse effects are bone marrow depression with neutropenia, anaemia and thrombocytopenia together with gastrointestinal toxicity, with nausea, vomiting, diarrhoea, stomatitis and constipation. Fatigue and fever have also been reported commonly.

Post-marketing experience:

Navelbine soft capsule is used as monotherapy or in combination with other chemotherapeutic agents such as cisplatin or capecitabin.

The system organ classes most affected in post-marketing experience are the “Haematological and lymphatic system disorders”, the “Gastrointestinal disorders” and the “general disorders and administration site abnormalities” This information is consistent with the pre-marketing experience.

- **Infections and infestations**

Very common: Bacterial, viral or fungal infections without neutropenia affecting different systems (respiratory, gastrointestinal, urinary) G1-4: 12.7%; G3-4: 4.4%.

Common: Bacterial, viral or fungal infections as a result of bone marrow depression or immunological disorder (infections associated with neutropenia) usually reversible with appropriate treatment.

Infections associated with G3-4 neutropenia: 3.5%.

Not known: Septic neutropenia.

Complicated septicaemia, occasionally fatal.

- **Blood and lymphatic system disorders**

Very common: Bone marrow depression, particularly causing neutropenia (G1-4: 71.5 %; G3: 21.8 %: G4 25.9%; reversible and representing 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 2.8% febrile neutropenia.

- **Metabolism and nutrition disorders**

Not known: Severe hyponatraemia

- **Psychiatric disorders**

Common: Insomnia G1-2: 2.8%.

- **Central nervous system disorders**

Very common Neuro-sensory disorders (G1-2: 11.1%) generally restricted 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%.

Altered taste G1-2: 3.8%.

Uncommon: Ataxia, G3: 0.3%.

- **Eye disorders**

Common: Visual disorders, G1-2: 1.3 %.

- **Cardiac disorders**

Uncommon: Heart failure and cardiac dysrhythmias.

Not known: Myocardial infarction in patients with history of cardiac disorders or risk factors.

- **Vascular disorders**

Common: Arterial hypertension G1-4 2.5 %; G3-4: 0.3 %.

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 %.

- **Gastro-intestinal disorders**

Very common: Nausea, G1-4: 74.7 %; G3-4: 7.3 %.

Vomiting, G1-4: 54.7 %; G3-4: 6.3 %; occurence of nausea and vomiting may be reduced with adjuvant treatment (oral setrons).

Diarrhoea, G1-4: 49.7 %; G3-4: 5.7 %.

Anorexia, G1-4: 38.6 %; G3-4: 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%. It may be appropriate to prescribe laxatives to patients with history of constipation and/or on concomitant treatment with morphine or morphine-mimetics.

Gastric disorders: G1-4: 11.7%.

Common: Oesphagitis, G1-3: 3.8 %; G3: 0.3 %. Dysphagia, G1-2: 2.3 %.

Uncommon: Paralytic ileus G3-4 (0.9%) [Exceptionally fatal]. Treatment can be restarted as bowel motility has returned to normal.

Not known: Gastrointestinal bleeding.

- **Hepatobiliary disorders**

Common: Hepatic disorders: G1-2: 1.3 %.

- **Skin and subcutaneous tissue disorders**

Very common: Alopecia G1-2 (29.4%), generally may occur and is generally mild.

Common: Skin reactions G1-2: 5.7 %.

- **Musculoskeletal and connective tissue disorders**

Common: Arthralgia, particularly jaw pain.

Myalgia (G1-4: 7 %; G3-4: 0.3 %).

- **Renal and urinary disorders**

Common: Dysuria, G1-2: 1.6 %.

Other genito-urinary disorders G1-2: 1.9 %.

- **General disorders and administration site abnormalities**

Very common: Fatigue/malaise G1-4: 36.7 %; G3-4: 8.5 %.

Fever, G1-4: 13.0 %; G3-4: 12.1 %.

Common: Pain, particularly at the site of the tumour. 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 %.

Adverse effects seen with Navelbine, concentrate for injection

Adverse effects have been seen with Navelbine, concentrate for injection during both pre- and post-marketing use whereas these have not been reported for Navelbine soft capsule.

In order to provide the most complete information as possible and to ensure improved safety of use of Navelbine soft capsule these effects are described below.

- **Infections and infestations**

Uncommon: Septicaemia (very occasionally fatal).

- **Immune system disorders**

Not known: Systemic allergic reactions such as anaphylaxis, anaphylactic shock or anaphylactoid reactions.

- **Endocrine disorders**

Not known: Syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

- **Vascular disorders**

Uncommon: Vasomotor flushes and cold extremities.

Rare: Severe hypotension and collapse.

- **Respiratory, thoracic and mediastinal disorders**

Uncommon: Like the other vinca alkaloids, administration of Navelbine has been associated with bronchospasm.

Rare: Occasionally fatal interstitial lung disease.

- **Gastro-intestinal 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

4.9. Overdose

Symptoms:

Navelbine overdose may cause bone marrow hypoplasia, occasionally associated with infection, fever, paralytic ileus and hepatic disorders.

Emergency procedure:

General symptomatic measures combined with blood transfusion, administration of growth factors and broad spectrum antibiotic therapy must be started if this is deemed necessary by the physician.

Appropriate close monitoring of hepatic function is recommended.

Antidote:

There is no known antidote in the event of Navelbine overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

Navelbine is a cytostatic antineoplastic agent belonging to the vinca alkaloid family although unlike the other vinca alkaloids the catharantine part of vinorelbine has been structurally modified. On a molecular level, it acts on the dynamic equilibrium of tubulin within the cell microtubular apparatus.

Navelbine inhibits tubulin polymerisation. It acts preferentially on the mitotic microtubules and only affects axonal microtubules at high concentrations. Its tubulin spiralising potential is less than that of vincristine.

Navelbine blocks mitosis in G2+M phase and causes cell death in interphase or at the subsequent mitosis.

The safety and efficacy of Navelbine have not been established in the paediatric population. Clinical data from two uncontrolled II studies (single arm) using vinorelbine as a solution for injection in 33 and 46 paediatric patients suffering from recurrent solid tumours including rhabdomyosarcomas, soft tissue sarcomas, Ewing's sarcomas, liposarcomas, synovial sarcomas, fibrosarcomas, central nervous system cancers, osteosarcomas and neuroblastomas at doses of 30 or 33.75 mg/m² on days 1 and 8

every 3 weeks or once per week for 6 weeks every 8 weeks did not show significant clinical efficacy. The toxicity profile is similar to that reported for adult patients (see section 4.2).

5.2. Pharmacokinetic properties

The pharmacokinetic parameters of vinorelbine have been evaluated in blood.

Absorption

Following oral administration, Navelbine is rapidly absorbed with a T_{max} achieved at 1.5 to 3 h and a peak plasma concentration (C_{max}) of approximately 130 ng/ml after administration at the dose of 80 mg/m². Its absolute bio-availability is approximately 40% and vinorelbine exposure is not changed by simultaneous ingestion of food.

Oral vinorelbine administered at doses of 60 and 80 mg/m^2 results in similar blood exposure to the exposure with doses of 25 and 30 mg/m^2 of the intravenous form respectively.

Inter-individual variability of exposure is equivalent after IV and oral administration.

Blood exposure increased proportionately to dose at doses up to 100 mg/m².

Distribution:

Plasma protein binding is low (13.5%), although vinorelbine is highly bound to blood cells, particularly to platelets (78%).

The steady state volume of distribution is large, on average 21.2 l.kg^{-1} (range 7.5 - 39.7 l.kg^{-1}) indicating an extensive tissue distribution.

Extensive amounts of vinorelbine enter lung tissues as shown by the mean tissue/serum concentration ratio found from surgical lung biopsy, which is over 300.

Vinorelbine has not been found in the central nervous system.

Biotransformation

All of the metabolites of vinorelbine are formed by the cytochrome P450 CYP3A4 isoform, except for the 4-O-deacetyl-vinorelbine which appears to be formed by carboxylesterases. 4-O-deacetyl-vinorelbine is the only active metabolite and the main metabolite found in blood.

No sulphate or glucuronide conjugates have been detected.

Elimination

The elimination half-life of vinorelbine is approximately 40 hours. Blood clearance is high similar to hepatic blood flow, and is 0.72 l.h^{-1}/kg^{-1} (range: 0.32 to 1.26 l.h^{-1}.kg^{-1}).

Renal elimination is low (<5% of the dose administered) and it is mostly the unchanged substance which is found. Biliary excretion is the main elimination route, both as metabolites and as unchanged vinorelbine (main compound found).

Special populations

Renal impairment

The effects of renal dysfunction on vinorelbine elimination have not been studied. In view of the low renal elimination of vinorelbine a reduction in dose is not indicated in patients with low level of renal elimination.

Liver impairment

The pharmacokinetics of oral vinorelbine were not changed after administration of a dose of 60 mg/m²/week in mild hepatic disorder (bilirubin < 1.5 x ULN, and AST and/or ALT 1.5 to 2.5 x ULN), and the dose of 50 mg/m²/week in moderate hepatic disorder (bilirubin 1.5 to 3 X ULN, regardless of ALT or AST level). Navelbine soft capsule has not been studied in patients suffering from severe hepatic disorder and its use is therefore not recommended in these patients (see sections 4.2 and 4.4)

Elderly patients:

A study of oral vinorelbine administration to elderly patients (> 70 years old) suffering from NSCLC showed that age does not influence the pharmacokinetics of vinorelbine.

As elderly people are frail, however, caution is required when doses of Navelbine are increased (see section 4.2).

Relationships between pharmacokinetics and pharmacodynamics

A close correlation has been found between blood exposure and leukocyte and depletion of leukocytes or neutrophils.

5.3. Preclinical safety data

Mutagenic and carcinogenic potential

Binding of NAVELBINE to the achromatic spindle during mitosis may cause incorrect chromosome distribution. In animal studies, intravenous NAVELBINE cause aneuploidy and polyploidy. It is possible that NAVELBINE may also cause mutagenic effects (induction of aneuploidy) in human beings.

Carcinogenicity studies in which NAVELBINE was administered intravenously once every two weeks in order to avoid the toxic effects of the substance were negative.

Reproduction studies

NAVELBINE has been shown to be embryo and foeto-lethal and teratogenic in animal reproduction studies. The no adverse effect level in the rat was 0.26 mg/kg every 3 days.

After peri-or postnatal administration of a dose of 1.0 mg/kg IV every 3 days to the rat, delayed weight gain was seen in the offspring until the 7th week of life.

Pharmacological safety

No haemodynamic effects have been found in dogs which receive vinorelbine at the maximum tolerated dose: only minor non significant repolarisation disturbances were seen, as applies to the other vinca alkaloids tested. No cardiovascular system effects were seen in primates which received repeated doses of Navelbine for 39 weeks.

Overdose in animals

The symptoms of overdose in animals tested consisted of hair loss, abnormal behaviour (prostration, drowsiness), pulmonary lesions, weight loss and various degrees of bone marrow aplasia.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Anhydrous ethanol
Purified water
Glycerol,
Macrogol 400

Capsule shell: gelatine, 85 per cent glycerol, sorbitol/sorbitans (Anidrisorb 85/70), red (for 30mg capsule) or yellow (for 20mg capsule) iron oxide (E172), titanium dioxide (E171), medium chain triglycerides, PHOSAL 53 MCT (phosphatidylcholine, glycerides, ethanol).

Edible printing ink: E120, hypromellose, propylene glycol.

6.2. Incompatibilities:

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Store at temperatures between +2° C and +8° C (in a refrigerator)

Store the original container properly closed.

6.5. Nature and content of container

1 capsule in blister sheet (PVC/PVDC/Aluminium)

6.6. Special precautions for disposal and other handling

NAVELBINE soft capsule should be swallowed with water and the capsule should be neither chewed not sucked. It is recommended that the capsule is taken at the end of a meal.

NAVELBINE soft capsule must be administered orally strictly.

For safety reasons, all unused or damaged capsules should be returned to the prescriber or pharmacist in order to be destroyed in accordance with the current procedure for cytotoxic substances.

For details on the use and handling of Navelbine soft capsule:

To open the secure packaging:

- cut the blister with scissors along the black dotted line,
- gently peel the white plastic foil which covers the blister,
- Push the transparent plastic to expel 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

8. MARKETING AUTHORISATION NUMBER(S)

1 capsule in blister sheet (PVC/PVDC/Aluminium)
- 20 mg: 34009 365 948 4 5
- 30 mg: 34009 365 949 0 6

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/01/2001 - 22/02/2006.

10. DATE OF REVISION OF THE TEXT

July 2016

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS:

Not applicable.

PRESCRIBING AND SUPPLY CONDITIONS

List I

Medicinal product subject to hospital prescription. Prescription restricted to specialists in oncology or haematology or to physicians accredited in cancerology. Medicinal product requiring specific monitoring during treatment.

A patient information and follow up booklet is provided by the Marketing Authorisation holder.