ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NAVELBINE 10 mg/1 ml, solution for injection in a vial

NAVELBINE 50 mg/5 ml, solution for injection in a vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vinorelbine ditartrate..... 13.85 mg
Amount equivalent to vinorelbine ..... 10.00 mg
Per 1 ml of solution for injection.

Vinorelbine ditartrate…….. 69.25 mg

Amount equivalent to vinorelbine ..... 50.00 mg

Per 5 ml of solution for injection.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
Navelbine is a clear colourless to slightly yellow solution with a pH of between 3.3 and 3.8.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- non-small cell lung cancer
- metastatic breast cancer

4.2. Posology and method of administration

Strictly for intravenous use only after appropriate dilution.

Intrathecal administration of Navelbine may be fatal.

Instructions for use and handling: see section 6.6.

It is recommended that Navelbine will be infused over a short period of time of 6 to 10 minutes after dilution in 20 to 50 ml of a 9 mg/ml (0.9%) sodium chloride solution for injection or a 5% glucose solution for injection.

Following administration the vein must always be rinsed with a minimum of 250 ml of physiological solution.

In monotherapy the usual dose is 25 to 30 mg/m² administered weekly.

In combination chemotherapy the usual dose (25 to 30 mg/m²) is generally continued, whereas the administration frequency is reduced; for example administration on D1 and D5 every 3 weeks or D1 and D8 every 3 weeks, depending on the protocol.

Administration in the elderly:

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

Administration in patients suffering from liver insufficiency:

The pharmacokinetics of Navelbine are unchanged in patients with moderate or severe liver insufficiency. However, as a precautionary measure, it is recommended that the dose be reduced to 20 mg/m² and that haematological parameters be monitored in patients suffering from severe liver insufficiency (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.

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).

4.3. Contraindications

This medicine is contraindicated in the following situations:

- Known hypersensitivity to vinorelbine or other vinca alkaloids or to any other constituent of Navelbine.
- Neutrophil count under 1500/mm^3 or severe current or recent infection (within 2 weeks).
- Platelet count < 100000/mm^3.
- Breastfeeding (See section 4.6)
- In combination with the yellow fever vaccine.

4.4. Special warnings and precautions for use

Special warnings

Navelbine must be administered under the supervision of a physician experienced in the use of chemotherapy.

As the main risk associated with Navelbine is the inhibition of the hematopoietic system, treatment should be given under strict haematological monitoring before any new injection (measurement of haemoglobin, leukocyte, neutrophil and platelet counts on each day the product is administered).

The limiting toxicity is neutropenia. This non-cumulative effect reaches a nadir between the 7th and 14th day after administration and reverses rapidly in the subsequent 5 to 7 days.

Administration must be delayed until parameters have returned to normal if the neutrophil count is under 1500/mm^3 and/or platelet count is under 100000/mm^3,

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

Special precautions for use

Increased caution is recommended in all patients with history of ischaemic heart disease (see section 4.8).

The pharmacokinetics of Navelbine are unchanged in patients with severe or moderate liver insufficiency. For dosage adjustment in this group of patients, refer to section 4.2.

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

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

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

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).

Avoid any accidental contamination with the eye. Risk of severe irritation or even ulceration of the cornea if the substance is sprayed under pressure. In the event that the substance comes into contact with the eye, wash immediately with a 9 mg/ml (0.9%) sodium chloride solution for injection.

Increased caution is required in Japanese patients as cases of interstitial lung disease have been reported more frequently in this population.

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

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 (see section 4.4).

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.

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.

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 adverse reactions reported as non-isolated cases are listed below by System organ class and incidence.

Incidences are defined as follows: 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), according to the MedDRA incidence convention and system organ classification.

The adverse reactions reported most commonly are: bone marrow depression with neutropenia, anaemia, neurological disorders, gastrointestinal toxicity with nausea, vomiting, stomatitis and constipation, transient rises in liver enzymes, alopecia and local phlebitis.

Additional adverse reactions from Post Marketing Experience have been added using the MedDRA classification with an unknown incidence.

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 cases reported

Detailed information:
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).

Infections and infestations:

Common:
- Bacterial, viral or fungal infection at different sites (respiratory, urinary, gastrointestinal etc.), mild to moderate in intensity and usually reversing with appropriate treatment.

Uncommon:
- Severe sepsis with organ failure.
- Septicaemia

Very rare:
- Complicated septicaemia, occasionally fatal.

Not known:
- Septic neutropenia.

Blood and lymphatic system disorders

Very common:
- Bone marrow depression, particularly causing neutropenia (G3: 24.3% ; G4: 27.8%), reversible within 5 to 7 days and not cumulative over time.
- Anaemia (G3-4: 7.4%)

Common:
- Thrombocytopenia (G3-4: 2.5%), rarely severe.

Not known:

- Febrile neutropenia.
- Pancytopenia.

Immune system disorders

Not known:

- Systemic allergic reactions such as anaphylaxis, anaphylactic shock or anaphylactoid reaction.

Endocrine disorders

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

Metabolism and nutrition disorders

Rare:
- Severe hyponatraemia

Not known:
- Anorexia

Nervous system disorders

Very common:
- Neurological disorders (G3-4: 2.7%) including loss of deep tendon reflexes.
- Cases of lower limb weakness have been reported after prolonged treatment.

Uncommon:
- Severe paraesthesiae with sensory and/or motor abnormalities.

These effects generally reverse when treatment is stopped.

Cardiac disorders

Rare:
Ischaemic heart disease (angina pectoris, myocardial infarction, occasionally fatal)

Very rare:
- Tachycardia, palpitations and cardiac dysrhythmias.

Vascular disorders

Uncommon:
- Hypotension, hypertension, vasomotor flushes and cold extremities.

Rare:
- Severe hypotension, collapse.

Respiratory, thoracic and mediastinal disorders

Uncommon:
- Like the other vinca alkaloids, Navelbine is liable to cause dyspnoea and bronchospasm.

Rare:
- Occasionally fatal interstitial lung disease.

Gastro-intestinal disorders

Very common:
- Stomatitis (G1-4: 15% with Navelbine monotherapy).
- Nausea, vomiting (G 1-2: 30.4% and G 3-4: 2.2%). Occurence of nausea and vomiting may be reduced with anti-emetic treatment.
- Constipation is the main symptom (G3-4: 2.7%) which progresses rarely to paralytic ileus with Navelbine in monotherapy and (G3-4: 4.1%) with Navelbine in combination with other cytotoxics.

Common:
- Diarrhoea, usually mild to moderate.

Rare:
- Paralytic ileus: treatment can be restarted as bowel motility has returned to normal.
- Pancreatitis

Hepatobiliary disorders

Very common:
- Transient rises in liver enzymes (G 1-2) without clinical symptoms (AST 27.6% and ALT 29.3%).

Skin and subcutaneous tissue disorders

Very common:
- Generalised alopecia, mild in severity (G3-4: 4.1% in monotherapy).

Rare:
- Generalised cutaneous reactions

Not known:
- Palmo-plantar erythrodysesthesia.

Musculoskeletal and connective tissue disorders

Common:
- Arthralgia, including jaw pain and myalgia.

General disorders and administration site abnormalities

Very common:
- Injection site reactions may involve erythema, burning sensations, discolouration of the vein and localised phlebitis (G3-4: 3.7% with Navelbine monotherapy).

Common:
- Asthenia, fatigue, fever, pain at various sites including chest pain and pain at the tumour site have been reported in patients receiving Navelbine.

Rare:
- Local necrosis . These effects may be reduced by proper positioning of the needle or catheter in the vein and bolus injection followed by rinsing the vein.

Reporting of side effects

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 and paralytic ileus.

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.

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, Navelbine acts on 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.

Distribution:

The steady-state volume of distribution is large 21.2 l/kg (range: 7.5-39.7 l/kg), characteristic of extensive tissue distribution.

Plasma protein binding is low (13.5%). Vinorelbine binds strongly to blood cells, particularly to platelets (78%).

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. The metabolism of vinorelbine does not involve either sulphate or glucuronide conjugation.

Elimination

The mean elimination half-life of vinorelbine is approximately 40 hours. The total clearance is high. 0.72 $l.h^{-1}.kg^{-1}$ (range: 0.32-1.26 $l.\ h^{-1}.kg^{-1}$) and approaching liver blood flow. Renal excretion is low (< 20% of dose administered and is mostly in the unchanged form. Biliary excretion is the predominant route of excretion in the form of unchanged vinorelbine which is the main compound found, and its metabolites.

Special populations

Patients with renal and liver insufficiency

Although the impact of renal dysfunction on the elimination of vinorelbine has not been assessed, there is no reason to reduce dosage in patients with renal insufficiency as the renal elimination of vinorelbine is low**.**

The effect of liver impairment on the pharmacokinetics of vinorelbine was firstly studied in patients suffering from liver metastases from a breast cancer. This study concluded that a change in clearance was only seen when liver invasion was over 75%. A phase 1 study has also been conducted in patients with hepatic dysfunction: 6 patients with moderate impairment (serum bilirubin ≤ 2 times the ULN and transaminases ≤ 5 times the ULN) treated at the maximum dose of 25 mg/m2 and 8 patients with severe impairment (serum bilirubin > 2 times the ULN and/or transaminases > 5 times the ULN) treated at the maximum dose of 20 mg/m2. Total clearance in these patients was similar to that of patients with normal liver function and indicated that the pharmacokinetics of vinorelbine are not altered in liver insufficiency regardless of extent. As a precautionary measure, however, it is recommended that the dosage be reduced to 20 mg/m² and that haematological indices be monitored closely in patients suffering from severe liver insufficiency.

Elderly patients

A study conducted on Navelbine in elderly people (≥ 70 year old) suffering from non-small cell lung cancer showed that the pharmacokinetic parameters of vinorelbine were not altered with age. As elderly people are frail, however, caution is required when doses of Navelbine are increased (see section 4.2).

Pharmacodynamic/pharmacokinetic correlation
A close correlation has been found between blood vinorelbine exposure and both leucopenia and neutropenia.

5.3. Preclinical safety data

Mutagenic and carcinogenic potential

Vinorelbine causes chromosomal damage but was not mutagenic in the Ames test.
It is accepted that Navelbine may cause mutagenic effects (induction of aneuploidy and polyploidy) in human beings.

Reproductive toxicity studies

Animal reproductive studies have shown that Navelbine was embryo foeto-lethal and caused teratogenic effects.

Pharmacological safety

No haemodynamic effects have been found in dogs which received vinorelbine at the maximum tolerated dose: only minor non significant repolarisation disturbances were seen, as applies to the other vinca alkaloids.

No cardiovascular system effects were seen in primates which received repeated doses of Navelbine for 39 weeks.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Water for solution for injection.

6.2. Incompatibilities

Navelbine must not be diluted in alkaline solutions (risk of precipitation).
This medicinal product must not be mixed with other medicinal products except for those listed in section 6.6.

6.3. Shelf life

Before opening. 3 years
After Navelbine has been diluted in a 9 mg/ml sodium chloride (0.9%) solution for injection or a 5% glucose solution for injection, the diluted solution has been shown to be physico-chemical stable for 8 days at room temperature (20°C +/- 5°C) or in a refrigerator (+2°C to +8°C) protected from light in a neutral glass bottle or PVC or vinyl acetate bag.
From a microbiological point of view, however, the substance should be used immediately. If not used immediately the storage times and conditions after dilution and before use are the responsibility of the user alone and should not exceed 24 hours at a temperature of between +2°C à to 8°C, unless the dilution is carried out under appropriately monitored and validated aseptic conditions.

6.4. Special precautions for storage

Store in a refrigerator (between +2°C and +8°C) and in its original external packaging protected from

light (See section 6.3).
Do not freeze

6.5. Nature and content of external packaging

1 ml or 5 ml in glass vial (type I) closed by a butyl or chlorobutyl stopper. The stopper is covered with an aluminium cap; box of 1 and 10 bottles.

6.6. Special precautions for disposal and other handling

Navelbine must be prepared and administered by trained staff. Protective glasses, disposable gloves, disposable surgical mask and disposable apron must be worn. Any accidental spillage or leakage of the substance must be wiped up.
In the event that the substance comes into contact with the eye, immediately wash thoroughly for a long period of time with a 0,9% sodium chloride solution for injection. In the event of accidental spillage onto skin, wash thoroughly with water and then gentle soap and then rinse thoroughly for a long period of time.
Once prepared, all surfaces exposed to the substance must be appropriately cleaned and both hands and faces should be cleaned.
No container/contents interaction occurs between Navelbine and neutral glass bottle, PVC bag, vinyl acetate bag or infusion kit with PVC tube.
It is recommended that Navelbine be infused over a short period of time of 6 to 10 minutes after dilution in 20 to 50 ml of a 0.9% sodium chloride solution for injection or a 5% glucose solution for injection. Following administration, the vein should be appropriately rinsed with at least 250 ml of isotonic solution.

Navelbine must strictly be administered by intravenous route only. It is extremely important to ensure that the needle is correctly introduced into the vein before beginning the injection. In the event of extravasation: severe local irritation may occur if the substance passes outside of the vein (subcutaneous tissue) into the surrounding tissue during administration. In this case the injection should be stopped immediately, the vein rinsed with saline solution and as much of the extravasated substance aspirated as possible. The remaining amount should be administered through another venous access. Application of moderate heat facilitates diffusion of the substance and appears to reduce the risk of cellulitis. In the event of extravasation, in order to reduce the risk of phlebitis, IV glucocorticoids may be administered immediately. Pregnant women should be alerted and avoid handling cytotoxic agents.
Before being administered, solutions for injection must be inspected visually to detect any presence of particles or discolouration.
Any unused medicinal products or waste must be disposed of in accordance with current regulations.

7. MARKETING AUTHORISATION HOLDER

PIERRE FABRE MEDICAMENT
45, PLACE ABEL GANCE
92100 BOULOGNE

8. MARKETING AUTHORISATION NUMBER(S)

- 34009 331 903 8 5: 1 ml in bottle (glass).
- 34009 331 904 4 6: 1 ml in bottle (glass), box of 10

- 34009 331 844 1 4: 5ml in bottle (glass).
- 34009 331 845 8 2: 5ml in bottle (glass), box of 10

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/04/1989

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.