Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

NAVELBINE 10 mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Vinorelbine 10 mg/ml as vinorelbine tartrate.

Each 1ml vial contains 10 mg Vinorelbine as vinorelbine tartrate
Each 4ml vial contains 40 mg Vinorelbine as vinorelbine tartrate
Each 5ml vial contains 50 mg Vinorelbine as vinorelbine tartrate
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion. Navelbine is a clear, colourless to pale yellow solution with a pH of 3.3 – 3.8

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vinorelbine is indicated in adult patients for treatment of:

- advanced non-small-cell lung cancer as monotherapy or in combination with other chemotherapy
- as adjuvant treatment of non-small-cell lung cancer in combination with platinum-based chemotherapy
- advanced breast cancer as monotherapy or in combination with other agents.

4.2 Posology and method of administration

Intra-thecal administration of Navelbine may be fatal.
Navelbine must only be administered by the intravenous route as an infusion over 6 – 10 minutes.
Instructions for use and handling: see section 6.6.

Administration
- It is recommended to infuse Navelbine over 6 to 10 minutes after dilution in a 50 ml infusion bag with sodium chloride 9 mg/ml (0.9%) solution for injection or in 5% glucose solution for injection.
- The infusion time of 6 to 10 minutes must be followed as the risk of venous irritation is increased if the infusion exposure time is increased.
- Administration should always be followed with at least 250 ml of a normal saline infusion to flush the vein to avoid the risk of venous irritation.
- It is vital to ensure that the cannula is accurately placed in the vein before starting to infuse Navelbine. If the drug extravasates into the surrounding tissue during the administration considerable local irritation may occur. In this case, the administration should be stopped, the vein flushed with 0.9 % sodium chloride solution and the remaining dose administered in another vein.

The management of any extravasation should be according to local hospital guidelines and policies.

Advanced non-small cell lung cancer and advanced breast cancer
- In monotherapy the usual dose given is 25-30 mg/m^2 once weekly.
- In combination chemotherapy the usual dose (25-30 mg/m^2) is usually maintained, while the frequency of administration is reduced e.g. day 1 and 5 every 3 weeks or day 1 and 8 every 3 weeks according to treatment protocol.

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 patients with liver insufficiency
The pharmacokinetics of Navelbine is not modified in patients presenting with moderate or severe liver impairment. Nevertheless as a precautionary measure a reduced dose of 20mg/m^2 and close monitoring of haematological parameters is recommended in patients with severe liver impairment, (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 renal insufficiency, (see sections 4.4, 5.2).

Administration in children
Safety and efficacy in children have not been established and administration is therefore not recommended, (see section 5.1).

4.3 Contraindications

- Known hypersensitivity to vinorelbine or other vinca alkaloids, or to any of the excipients.
- Neutrophil count < 1500/mm^3 or severe infection current or recent (within 2 weeks)
- Platelet count < 100000/mm^3
- In combination with yellow fever vaccine, (see section 4.5).
- Lactation, (see section 4.6).

4.4 Special warnings and precautions for use

Special warnings

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

Since inhibition of the hematopoietic system is the main risk associated with Navelbine, close haematological monitoring should be undertaken during treatment (determination of haemoglobin level and the leukocyte, neutrophil and platelet counts on the day of each new administration).

The dose limiting adverse reaction is mainly neutropenia. This effect is non-cumulative, having its nadir between 7 and 14 days after the administration and is rapidly reversible within 5 to 7 days. 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.

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 history of ischemic heart disease, (see section 4.8).

The pharmacokinetics of Navelbine is not modified in patients presenting moderate or severe liver impairment, (see section 5.2). For dosage adjustment in this specific patient group, (see section 4.2).

As there is a low level of renal excretion there is no pharmacokinetic rationale for reducing the dose of Navelbine in patients with impaired kidney function, (see sections 4.2, 5.2).

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

This 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 Navelbine 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.

All contact with the eyes should be strictly avoided. There is a risk of severe irritation and even corneal ulceration if the drug is sprayed under pressure. Immediate washing of the eye with normal saline solution should be undertaken if any contact occurs.

Pulmonary toxicity, including severe acute bronchospasm, interstitial pneumonitis, acute respiratory distress syndrome (ARDS) occurring with the use of Navelbine intravenous pharmaceutical form, has been reported. The mean time to onset of ARDS after vinorelbine administration was one week (range 3 to 8 days).

The infusion must be immediately interrupted in patients who develop unexplained dyspnea or have any evidence of pulmonary toxicity.

Interstitial lung disease has been reported more frequently in the Japanese population. Special attention should be exercised for this specific population.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use contraindicated
Yellow fever vaccine: as with all cytotoxics, risk of fatal generalised vaccine disease, (see section 4.3).

Concomitant use not recommended
Live attenuated vaccines: (for yellow fever vaccine, see concomitant use contraindicated) as with all cytotoxics, 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 (e.g. poliomyelitis) (see section 4.4).

Phenytoin: as with all cytotoxics, 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.

Itraconazole: as with all vinca-alkaloids, increased neurotoxicity of vinca-alkaloids due to the decrease of their hepatic metabolism.

Concomitant use to take into consideration
Cisplatin: 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.

Mitomycin C: risk of bronchospam and dyspnoea are increased, in rare case an interstitial pneumonitis was observed.

Ciclosporin,tacrolimus:excessive immunodepression with risk of lymphoproliferation.

As vinca alkaloids are known 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.

The combination of Navelbinewith other drugs with known bone marrow toxicity is likely to exacerbate the myelosuppressive adverse effects.

As CYP3A4 is mainly involved in the metabolism of vinorelbine, combination with strong inhibitors of this isoenzyme (e.g. azole antifungals such as ketoconazole and 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.

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.

Anticoagulant treatment: as with all cytotoxics, the frequency of INR (International Normalised Ratio) monitoring should be increased due to the potential interaction with oral anticoagulants and increased variability of coagulation in patients with cancer.

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 / contraception in males and females
Due to the genotoxic potential of vinorelbine (see section 5.3), women of child-bearing potential should use effective contraception during therapy with vinorelbine and for 7 months after treatment.

Men should use effective contraception during treatment with vinorelbine and for 4 months after treatment.

As vinorelbine is genotoxic, genetic counselling is also recommended for those wishing to conceive after therapy.

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 child cannot be excluded therefore breast feeding must be discontinued before starting treatment with Navelbine, (see section 4.3).

Fertility:
Men being treated with Navelbine are advised not to father a child during treatment and for 4 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.

On the basis of the vinorelbine pharmacodynamic profile, Navelbine is unlikely to impair the ability to drive or operate machinery. However, caution is necessary in patients treated with Navelbine considering some side effects of the drug: see section 4.8.

4.8 Undesirable effects

Adverse reactions reported as more than isolated cases are listed below, by system organ class and by the MedRA 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*.

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), including isolated reports
Not known	Post marketing reports

The most commonly reported adverse drug reactions are bone marrow depression with neutropenia, leucopenia and anaemia, neurologic disorders, gastrointestinal toxicity with nausea, vomiting, stomatitis and constipation, transient elevations of liver function tests, alopecia and local phlebitis.

Detailed Adverse reactions information:
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).

Infections and infestations
Common: Infection bacterial, viral or fungal at different sites, mild to moderate and usually reversible with an appropriate treatment.
Uncommon: Severe sepsis sometimes with other organ failure. Septicaemia.
Very rare: Complicated septicaemia and sometimes fatal.
Not known: Neutropenic sepsis, Neutropenic infection G3-4

Blood and lymphatic system disorders
Very Common: Bone marrow depression resulting mainly in neutropenia (G3: 24.3%; G4: 27.8%), reversible within 5 to 7 days and non-cumulative over time. Anaemia (G3-4: 7.4%).
Common: Thrombocytopenia (G3-4: 2.5%) may occur but are seldom severe.
Not known: Febrile neutropenia. Pancytopenia, Leucopenia G1-4

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

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

Metabolism and nutrition disorders
Rare: Severe hyponatraemia.
Not known: Anorexia.

Nervous system disorders
Very Common: Neurologic disorders (G 3-4: 2.7%) including loss of deep tendon reflexes. Weakness of the lower extremities has been reported after a prolonged chemotherapy.
Uncommon: Severe paresthesias with sensory and motor symptoms are infrequent
These effects are generally reversible.
Not known: Headache, Dizziness, Ataxia, Posterior reversible encephalopathy syndrome

Cardiac disorders
Rare: Ischemic heart disease: angina pectoris, myocardial infarction
Very rare: Tachycardia, palpitation and heart rhythm disorders
Not known: Heart failure

Vascular disorders
Uncommon: Hypotension, hypertension, flushing and peripheral coldness.
Rare: Severe hypotension, collapse.

Respiratory system, thoracic and mediastinal disorders
Uncommon: Dyspnoea and bronchospasm may occur in association with Navelbine treatment as with other vinca alkaloids.
Rare: Interstitial pneumonopathy sometimes fatal has been reported.
Not Known: Cough G1-2, Acute respiratory distress syndrome sometimes fatal, Pulmonary embolism

Gastrointestinal disorders
Very Common: Stomatitis (G1-4: 15%, with Navelbine as single agent). Nausea and vomiting (G 1-2: 30.4% and G 3-4: 2.2%). Anti-emetic therapy may reduce their occurrence. Constipation is the main symptom (G 3-4: 2.7%,) which rarely progresses to paralytic ileus with Navelbine as single agent and (G3-4: 4.1%), with the combination of Navelbine and other chemotherapeutic agents.
Common: Diarrhoea usually mild to moderate may occur.
Rare: Paralytic ileus, treatment may be resumed after recovery of normal bowel mobility. Pancreatitis has been reported.
Not known: Gastrointestinal bleeding, Severe diarrhoea, Abdominal pain.

Hepatobiliary disorders
Very Common: Transient elevations of liver function tests (G1-2) without clinical symptoms were reported (SGOT in 27.6% and SGPT in 29.3%).
Not known: Hepatic disorder.

Skin and subcutaneous tissue disorders
Very Common: Alopecia, usually mild in nature, may occur, (G3-4: 4.1% with Navelbine as single chemotherapeutic agent).
Rare: Generalized cutaneous reactions have been reported with Navelbine Not known: Palmar-plantar erythrodysesthesia syndrome. Skin hyperpigmentation (serpentine supravenous hyperpigmentation)

Musculoskeletal and connective tissue disorders
Common: Arthralgia including jaw pain and myalgia

General disorders and administration site conditions
Very Common: Reactions at the injection site may include erythema, burning pain, vein discoloration and local phlebitis (G 3-4: 3.7% with Navelbine as single chemotherapeutic agent).
Common: Asthenia, fatigue, fever, pain at different sites including chest pain and pain at the tumour site have been experienced by patients receiving Navelbine therapy.
Rare: Local necrosis has been observed. Proper positioning of the cannula in the vein before starting to infuse Navelbine followed by liberal flushing of the vein can limit these effects.
Not known: Chills G1-2.

Investigations
Not known: Weight loss.

For the oral formulation of Navelbine the following additional Adverse Drug Reactions were reported, taste disorder, visual impairment, insomnia, dysphagia, oesophagitis, weight gain, dysuria, other genitourinary symptoms.

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 HPRA Pharmacovigilance Website: www.hpra.ie

4.9 Overdose

Symptoms
Overdosage with Navelbine could produce bone marrow hypoplasia sometimes associated with infection, fever and paralytic ileus.

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.

Antidote
There is no known antidote for overdosage of Navelbine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vinca alkaloïds 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 tumours, including rhabdomyosarcoma, other soft tissue sarcoma, Ewing sarcoma, liposarcoma, synovial sarcoma, fibrosarcoma, central nervous system cancer, osteosarcoma, neuroblastoma, at doses of 30 to 33.75mg/m^2 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. (see section 4.2).

5.2 Pharmacokinetic properties

Pharmacokinetic parameters of vinorelbine were evaluated in blood.

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. Vinorelbine has high affinity for platelets and lymphocytes. Binding to plasma protein is low (13.5%). However, vinorelbine binds strongly to blood cells and especially to platelets. 78% of the total blood-bound vinorelbine was associated with platelets and 4.8% of the total blood-bound vinorelbine was associated with lymphocytes. There is significant uptake of vinorelbine in the lungs, as assessed by surgical lung biopsies, which showed concentrations up to 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 $l.h^{-1}.kg^{-1}$ on average (range: 0.32 – 1.26 $l.h^{-1}.kg^{-1}$). Renal elimination is low (< 20% of the intravenous dose administered) and consists mostly in parent compound. Biliary excretion is the predominant elimination route of unchanged vinorelbine, which is the main recovered compound, and its metabolites.

Special patient groups
Renal 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 due to the low renal elimination.

Liver impairment
A first study has reported the effects of liver impairment on vinorelbine pharmacokinetics. This study was performed in patients with liver metastases due to breast cancer, and concluded that a change in mean clearance of vinorelbine was only observed when more than 75% of the liver is involved.

A phase I pharmacokinetic dose-adjusted study was conducted in cancer patients with liver dysfunction: 6 patients with moderate dysfunction (Bilirubin < 2 x UNL and Transaminases < 5 x UNL) treated up to 25 mg/m^2 and 8 patients with severe dysfunction (Bilirubin > 2 x UNL and/or Transaminases >5 x UNL) treated up to 20 mg/m^2. Mean total clearance in these two subsets of patients was similar to that in patients with normal hepatic function. Therefore, the pharmacokinetics of vinorelbine

is not modified in patients presenting moderate or severe liver impairment. Nevertheless, as a precautionary measure a reduced dose of 20mg/m^{2}and close monitoring of haematological parameters is recommended in patient with severe liver impairment, (see sections 4.2 and 4.4).

Elderly patients
A study with Navelbine 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, (see section 4.2).

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

5.3 Preclinical safety data

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

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

In animal reproductive studies, Navelbine was embryo-feto-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 Navelbine over 39 weeks.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Vial before opening: 3 years.
After dilution:
After diluting Navelbine in 0.9% sodium chloride solution for injection or in glucose solution for injection 5% chemical and physical in-use stability has been demonstrated for 8 days at room temperature (+ 20° C ±□5° C) or in the refrigerator (2° C - 8° C) protected from light, in neutral glass bottle, PVC and vinyl acetate bags.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C unless preparation has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator at 2° C - 8° C. Do not freeze.
Store in the original container in order to protect from light.

Diluted solution, (see section 6.3).

6.5 Nature and contents of container

The drug is distributed in clear colourless glass vials (type I) of appropriate volume, closed by butyl or chlorobutyl stopper. The stopper is covered with a crimped-on aluminium cap equipped with a polypropylene seal.

Vials of 1, 4 and 5 ml.

Boxes containing 10 vials for each strength.
10 mg / 1 ml
40 mg / 4 ml
50 mg / 5 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only, discard any unused contents.

Handling and Use
The preparation and administration of Navelbine should be carried out by trained staff and as with all cytotoxic agents, precautions should be taken to avoid exposing staff during pregnancy.

Caution should be exercised in handling and preparing the Navelbine solution:

- Suitable eye protection, disposable gloves, face mask and disposable apron should be worn.

- Eventual spillage or leakage should be mopped up wearing protective gloves.

- All contact with the eye should be strictly avoided: risk of severe irritation and even corneal ulceration if the drug is sprayed under pressure. Immediate liberal washing of the eye with normal saline solution should be undertaken if any contact occurs.

- On completion, any exposed surface should be thoroughly cleaned and hands and face washed.

Preparation of the solution for infusion
Navelbine must be diluted prior to administration in a 50 ml volume of sodium chloride 9 mg/ml (0.9 %) solution for injection or in 5 % glucose solution for injection.
In case of polychemotherapy, Navelbine should not be mixed with other agents
There is no content / container incompatibility between Navelbine and neutral glass bottle, PVC bag, vinyl acetate bag or infusion set with PVC tubing.
Navelbine must only be administered by the intravenous route as an infusion.
For further instructions on administration: see section 4.2.
Disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Pierre Fabre Medicament
Les Cauquillous
Lavaur
81500
France

8 MARKETING AUTHORISATION NUMBER

PA0329/011/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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